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الجامعة الأردنيـة
كلية الدراسات العليا

التاريـــخ: / /

نموذج رقم (١٨)
اقرار والتزام بقوانين الجامعة الأردنية وأنظمتها وتعليماتها لطلبة الماجستير

أنا الطالب: هبة فؤاد عبداللطيف أحمد الرقم الجامعي: 8071374
التخصص: الصيدلة الكلية: الصيدلة

اعلن بأنني قد التزمت بقوانين الجامعة الأردنية وأنظمتها وتعليماتها وقراراتها السارية المفعول المتعلقة باعداد رسائل الماجستير والدكتوراة عندما قمت شخصيا" باعداد رسالتي / اطروحتي بعنوان:

Evaluation of an extended release multiparticulate Dosage form of a high dose, highly soluble drug model by active layering technique.

وذلك بما ينسجم مع الأمانة العلمية المتعارف عليها في كتابة الرسائل والأطاريح العلمية. كما أنني أعلن بأن رسالتي /اطروحتي هذه غير منقولة أو مستلة من رسائل أو أطاريح أو كتب أو أبحاث أو أي منشورات علمية تم نشرها أو تخزينها في أي وسيلة اعلامية، وتأسيسا" على ما تقدم فانني أتحمل المسؤولية بأنواعها كافة فيما لو تبين غير ذلك بما فيه حق مجلس العمداء في الجامعة الأردنية بالغاء قرار منحي الدرجة العلمية التي حصلت عليها وسحب شهادة التخرج مني بعد صدورها دون أن يكون لي أي حق في التظلم أو الاعتراض أو الطعن بأي صورة كانت في القرار الصادر عن مجلس العمداء بهذا الصدد.

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EVALUATION OF AN EXTENDED RELEASE MULTIPARTICULATE DOSAGE FORM OF A HIGH DOSE, HIGHLY SOLUBLE DRUG MODEL BY ACTIVE LAYERING TECHNIQUE.

By

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Dedication

To my father and to my mother;

God bless them

They are the reason of what I am now

To my wife;

For her love, trust and always believing in me.

To my brothers;

Without your support, this would never have been possible.

To my kids;

Sarah, Bushra, Noor, Shahd, ...

This work is dedicated to you all.

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List of Abbreviations

Number	Symbol/Abbreviation	Definition
1	DTZ	Diltiazem hydrochloride
2	µm	Micrometer.
3	ml	Milliliter.
4	RH	Relative humidity.
5	HCl	Hydrochloric acid.
6	TEC	Triethyl citrate
7	GI	gastrointestinal
8	CR	Controlled release
9	IR	Immediate release
10	HPMC	hydroxypropylmethylcellulose
11	MFT	Minimum film forming temperature
12	API	Active pharmaceutical ingredient
13	DSC	Differential scanning calorimetry
14	KIR	Kollicoat IR

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Abstract

The purpose of this work was to evaluate the possibility of manufacturing controlled release multilayered, multiparticulate delivery system of the high dose, highly water soluble drug Diltiazem Hydrochloride (DTZ). The delivery system was manufactured using the active layering onto ready-made sugar sphere cores and controlled release coating technique using a bottom-spray, Wurster column fluid bed.

Drug layering was achieved by spraying a clear solution of DTZ and the binding polymer (Kollicoat IR) onto the sugar cores.

Diltiazem HCl pellets with different Drug loadings (30, 60 & 120%) were manufactured efficiently by active layering. Kollicoat IR has been used in two concentration levels compared to the drug with drug: polymer ratio (1:5 & 2:5) without any effect on the loading efficiency.

The level of the polymer in the layering solution showed no effect on the process efficiency within the used ratios, and up to 120% solids could be loaded with high efficiency (96%).

The layered pellets with highest loading (120%) and lower Kollicoat IR content were chosen to be coated with different levels of the rate controlling polymer Kollicoat SR at different levels (8, 15 & 22%) with and without the use of a plasticizer (TEC 5%). In addition, the effect of curing on the finished delivery system was evaluated.

Dissolution in water has been carried out for core and coated pellets. Drug release from core pellets was immediate and complete within 15 minutes.
Dissolution results of the coated pellets showed that increasing the level of coating reduced the rate of release from the pellets. Also results showed that the addition of plasticizer slowed the drug release in comparison to formulations without a plasticizer.
The effect of curing was obvious in coatings without plasticizer, while plasticized coatings showed no curing effect. The effect of heat and moisture on the stability of the pellets dissolution was also evaluated. Results showed that if the coated pellets were exposed to elevated temperature and moisture, time dependent decrease in dissolution rate will occur.

INTRODUCTION

Therapeutic value and pharmaeconomic value have in recent years become major issues in defining health care priorities under the pressure of cost containment.

The improvement in drug therapy is not only dependent on the development of new chemical entities but also on introducing the already existing active substances in a new delivery system. The conventional types of drug delivery systems like tablets, capsules, suppositories and fast acting injections are known to provide a prompt release of the drug. Therefore, to achieve as well as to maintain the drug concentration within the therapeutically effective range needed for treatment, it is often necessary to take this type of drug several times a day, resulting in significant fluctuation in drug levels and bad patient compliance (Breimer, D. D. 1999). In all types of treatments, a major challenge is to define the optimal dose, time, rate, and site of delivery. The aim of the development of drug delivery techniques is to control the rate of drug delivery to sustain the duration of therapeutic activity and/or target the delivery of drug to a specific organ or tissue. Many investigations are still going on to apply the concepts of controlled delivery for a wide variety of drugs (Chien, Y. W. 1992).

1. Advantages & Disadvantages of Controlled Release products

The basic rationale for controlled drug delivery is to alter the pharmacokinetics of pharmacologically active moieties or modify the molecular structure and/or physiological parameters inherent in a selected route of administration.

It is desirable that the duration of drug action become a design property of a rate - controlled dosage form but not a property of the drug molecules ' inherent kinetic properties.

The rationale for development and use of controlled dosage forms may include one or more of the following arguments (Brannon - Peppas, L.1997):

- Decrease the toxicity and occurrence of adverse drug reactions by controlling the level of drug and/or metabolites in the blood at the target sites.
- Improve drug utilization by applying a smaller drug dose in a controlled – release form to produce the same clinical effect as a larger dose in a conventional dosage form.
- Control the rate and site of release of a drug that acts locally so that the drug is released where the activity is needed rather than at other sites where it may cause adverse reactions.
- Provide a uniform blood concentration and/or provide a more predictable drug delivery.
- Provide greater patient convenience and better patient compliance by significantly prolonging the interval between administrations.

However, there are also disadvantages attached to the use of controlled – release dosage forms. These include higher cost of manufacturing, poor in vitro/in vivo correlation, and the effective release period is influenced and limited by the gastrointestinal (GI) residence time (Kydoneieus, A. F. 1980).

2. Candidate drugs for Controlled Release formulations

Drug properties those are important to consider during development of IR dosage forms are metabolism, stability, permeability, and solubility (Wilson, C. G. 2000). In the development of controlled release (CR) formulations, these aspects are also important, but in addition they must be considered in relation to the different environments that the CR formulations meet during their passage through the gastrointestinal tract.

The pharmacokinetic half - life for a drug may give an indication of whether an IR or CR formulation is to be chosen. For drugs with short biological half-life (Less than 1 – 2 h), devices that continuously release the active substance are required (Wilson, C. G. (2000). For drugs with life times longer than about 10 h, CR formulations may not add any benefits

compared to immediate release (IR) formulations. However, for drugs with half – lives between these limits, CR formulations may be a good alternative to IR formulations.

The stability of a drug in the solid state or in aqueous solution is a critical parameter when selecting an appropriate manufacturing process. A drug in an oral CR formulation reaches aqueous environments with, for example, variations in pH (1– 8), ionic strength, and bile salt concentration, which requires high chemical stability of the drug. Furthermore, the substance should be stable not only against chemical degradation such as hydrolysis but also against enzymatic degradation (metabolism) during the passage from the lumen to the systemic blood circulation.

The drug is released from oral CR formulations along the whole gastrointestinal tract. This implies that, in contrast to IR formulations, drug permeability must be good along the whole gastrointestinal tract for drugs in CR formulations. Furthermore, the solubility and the dissolution rate of the drug are extremely important to consider, since these factors will directly influence the release rate for the drugs from CR formulations. The dissolution rate can be described as the fraction of dissolved material from a drug particle and, according to the Noyes – Whitney equation (Noyes, A. A., and Whitney, W. R. 1897).

$$J = \frac{D}{h}(C_s - C_b)$$

Where D is the drug diffusion coefficient, h is the thickness of the stagnant diffusion layer around the particles, and Cs and C_b are the concentrations of the drug at the particle surface and in the surrounding bulk media, respectively. For substances in their most stable solid - state form, the concentration Cs close to the particle surface is equal to the saturated concentration. However, when a substance is in a different polymorphic state or in an amorphous state, Cs can be larger than the saturation concentration.

3. Principles for Extended Drug Formulations:

The main principles related to Extended Release systems are:

(i) Insoluble matrix formulations

(ii) Soluble hydrophilic matrix formulations

(iii) Membrane - coated solid dosage forms

Drug release from all kinds of CR formulations starts with hydration of the formulation and water diffusion into the system. The presence of water in the formulation facilitates the start of the dissolution process of the drug, whereby the dissolved drug can be released from the formulations.

$$\frac{dM_t}{dt} = JA = \frac{DA}{h}(C_s - C_b)$$

Where Mt is the amount of active drug that is released at the time t, D is the drug diffusion coefficient, and J is the flux of the drug from the formulation. The other parameters in the above Equation have been adjusted to fit the drug release from the formulation and therefore A becomes the surface area of the releasing system in the Equation (e.g., the area of the membrane - coated tablet), h the diffusion path length, and Cs and C_b correspond to the concentration of the dissolved active drug at the surface of the drug formulation and in the bulk solution surrounding the CR device, respectively. Depending on the exact type of CR system, some modifications in the Equation may be needed to fully describe the drug release. One important factor in the equation is the difference in concentration (Cs − C_b), and Cb is often assumed to be zero due to release under so - called sink conditions. For active substances in their most stable solid state, the remaining concentration, Cs, is equal to the saturation concentration in that medium. However, as mentioned above, Cs can be oversaturated or depend on pH. This means that the drug release from formulations depends

on the solid - state properties and pKa of the drug as well as the pH to which the formulation is exposed. Since the pH varies along the gastrointestinal tract, the drug release will be dependent on the position of the formulation in this tract. Several attempts to avoid pH - dependent drug release have been made, for example, by including buffers (Riiset al. 2007).

3.1 Insoluble Matrix Tablets

3.1.1 Principles of Formulation and Release Mechanisms

Looking at the homepage of the U.S. Food and Drug Administration (FDA 2011) and searching for "insoluble matrix tablets" produces more than 259 hits, this indicates that this research area is still active.

The term insoluble matrix tablet refers to tablets in which the drug is embedded in an inert carrier that does not dissolve in the gastrointestinal fluids. The carrier material in insoluble matrix tablets can be based on insoluble lipids or polymers, both matrix builders whose function is to keep the matrix together during the passage through the gastrointestinal tract and thus prolong the diffusion path of the drug before it is released from the formulation. The drug can be dispersed or dissolved or both in a matrix carrier and, depending on the formulation, different mechanisms can be regarded to take place:

- Dissolved drug in the matrix diffuses through the matrix.
- Dissolved drug in the matrix diffuses through pores in the matrix.
- Dispersed drug dissolves and diffuses through the matrix.
- Dispersed drug dissolves and diffuses through pores in the matrix.

As early as 1963, Higuchi (Higuchi, T. 1963) derived an expression for drug release from insoluble matrix systems. In this historical paper, Higuchi derived two equations for two different geometries, the simple planar sheet matrix system with infinite area and spherical

pellets. Furthermore, two special cases were treated, one where the matrix is a homogeneous matrix without pores and another where the matrix contains pores. In the system without pores, the drug is assumed to diffuse through the homogeneous matrix. For matrix systems with pores the efficiency in transport through liquid - filled pores is greater than through the solid matrix carrier. Therefore, the main contribution to the drug release is transport in the pores. This is gained by penetration of the surrounding medium into the pores, where it dissolves the drug. The dissolved drug can diffuse through the pores and be released at the surface of the matrix. When the matrix contains a drug - filled network, water can diffuse and dissolve the drug, and this creates a pore structure. The most common types of insoluble matrix tablets are those containing pores. The drug - release depends on the solubility of the drug, the drug - loading concentration, and the diffusion coefficient, which is related to the molecular size of the drug. The area of the insoluble matrix tablet also affects the drug release and can be changed by altering the dimensions or the geometry of the tablet. The drug release from insoluble matrix tablets also depends on the porosity and pore structure of the tablet, and the drug release rate increases with increasing porosity.

For ideal CR formulations, the rate - limiting step for drug absorption is the release rate from the CR formulation. Thus, since the release rate from an insoluble matrix system depends on time, the concentration of drug in the blood plasma will also be time dependent and not constant, which may be a therapeutic drawback. Another factor influencing the concentration of drug in the blood plasma is the gastrointestinal transit times. When the transit times of the formulations vary, the reproducibility between different administration occasions in one patient will be low, and furthermore, great variation in the patient group may be obtained. However, these conclusions are valid for all CR formulations based on matrix systems and not limited to insoluble matrix systems only.

3.2 HYDROPHILIC MATRIX TABLETS

3.2.1 Principles of Formulation and Release Mechanisms

Hydrophilic matrix tablets are composed of an active substance, a hydrophilic polymer, release modifiers, lubricants, and glidants. The technology goes back to the mid - 1960s when Lapidus and Lordi (Lapidus, H., and Lordi, N. G.1966) and Huber et al. (Huber, H. E. et al.1966) determined the drug release from hydrophilic matrix systems. The release mechanism for this type of formulation starts with the wetting and hydration of hydrophilic matrix polymers and the formation of a highly viscous polymer layer around the tablet (Figure 1). This layer is often referred to as a gel layer. However, the gel layer surrounds the inner (more or less dry) part of the tablet and this part is called the core. In traditional hydrophilic tablets, the active substance particles are embedded in the matrix carrier. The dissolution process of the active substance can start when the carrier material has dissolved in water and formed the aqueous gel layer, since without exposure to water the active substance cannot dissolve. Therefore, the "dry" core will shield the active drug from dissolution, which is one reason for the extended drug release from this type of formulation.

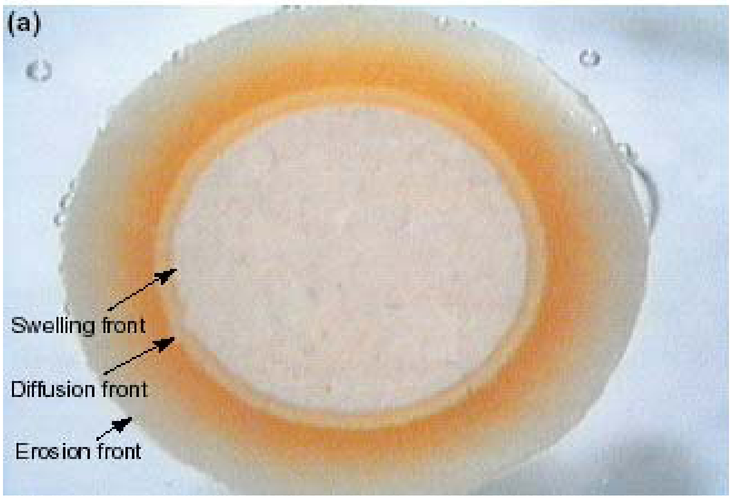


Figure 1. Clearly shows the three fronts during the swelling–dissolution process. From center to matrix periphery, the swelling front (polymer glassy–rubbery transition boundary), the diffusion front (solid drug–drug solution boundary) and the erosion front (swollen matrix–solvent boundary) can be identified.

The release process for hydrophilic matrix tablets can be schematically described as in Figure 1 (Colombo, P. et al. 2000). The figure shows a hydrophilic tablet undergoing wetting, swelling, and release. An interface between the solution and gel layer, here called the erosion front, can be identified, and the polymer chains and drug molecules are released at this front. In the gel layer, the polymer concentration will decrease from a highly concentrated solution at the swelling front, the interface between the gel layer and more or less dry core, to a diluted polymer solution at the erosion front (Koerner, A. et al. 2005).

At the same time, the water content in the gel layer gradually increases from the center of the tablet toward the erosion front, and thus the dissolution of the active substance particles can start already in the gel layer. However, the volume fraction of dissolved drug depends on the amount of available water, which in turn is a function of the position in the gel layer (Colombo, P. et al. 2000). Assuming that the drug saturation concentration is equal in water solutions and polymer gels, the volume fraction dissolved drug will correlate with the volume fraction water available, and the volume fraction drug will gradually increase with increasing distance from the core.

Far from the core, the variations in the concentration of polymer and water are less pronounced and, as long as solid particles co-exist with the saturated drug solution, the volume fraction of the drug will theoretically be almost constant. A third front has also been introduced, the diffusion front, which corresponds to the position in the gel layer where all of the active substance has dissolved. Between the swelling and dissolution front, dissolved and undissolved drug particles will coexist, but between the dissolution and erosion fronts, only dissolved drug molecules occur. In this region, the diffusion of drug out from the matrix will give rise to a decrease in the volume fraction of the drug.

The release process from hydrophilic matrix tablets depends on the properties of both the polymer and the drug. The swelling process is directly related to the properties of the

polymers, and this is an important factor for drug release, since the polymer swelling process can, for example, transport individual drug particles through the gel layer, which has been shown by Adler et al. (Adler, J. et al.1999). Macroscopically, polymer swelling can be observed as an increase in the size of the tablet. On a molecular level, the swelling depends on the dilution and transport of water into the gel layer.

This transport is driven by changes in the chemical potential, and the main contribution is the increase of conformational entropy when the polymer chains are diluted (Treloar, L. R. G.1975). The kinetics of the swelling process may vary. A faster polymer release rate compared to the swelling rate results in a movement of the erosion front toward the center of the tablet and the size of the tablet will diminish. Conversely, the tablet size increases when the polymer release is slower than the swelling process. When the swelling rate is on the same order as the polymer release rate, the position of the erosion front (i.e., tablet size) will remain constant.

The swelling front between the gel layer and amorphous (or semi crystalline) core material has traditionally been described as corresponding to a transition of the solid states of the polymers. The polymers in the core, for example in HPMC tablets, are in a glassy state, and the polymer material is transformed to a rubbery state due to the fact that water acts as a plasticizer and decreases the glass transition temperature (Siepmann, J. et al.1999). This rubbery state can be regarded as a polymer solution, and therefore the glassy - to - rubbery state transition can be regarded as a dissolution process of the polymer, where the dissolution rate will determine the position of the swelling front. A commonly described special case for hydrophilic tablets is the so – called front synchronization, which is when the movements of the swelling front and the erosion front occur equally fast. This special case corresponds to a constant gel layer thickness. Depending on the drug solubility and the dissolution, swelling, and release processes of the polymer, either of two different drug mechanisms can be

observed: erosion - or diffusion - controlled drug release. One way to characterize these two mechanisms is to compare the drug and the polymer release. The erosion mechanism is characterized by equal release of the polymer and the drug, whereas when the release of the drug is faster than that of the polymer, this is called diffusion- controlled drug release (Colombo, P. et al. 2000). The diffusion - controlled mechanism occurs when the diffusion front, the border between undissolved and dissolved drug, is displaced in the gel layer and the drug can efficiently diffuse out from the gel layer. The erosion mechanism dominates when the diffusion and erosion fronts overlap. This means that drug particles may be released from the surface of the gel layer. When this occurs, the drug particles will dissolve faster in the free solution than in the gel layer due to the fact that stirring is more efficient in the free solution, which results in a decreased thickness of the unstirred boundary layer around the particles and thus an increased dissolution rate. Whether the release mechanism will be diffusion or erosion controlled depends on:

(i) The polymer release rate, which governs the position of the rate erosion front, and

(ii) The drug dissolution rate, which governs the position of the diffusion front.

The position of the diffusion front and the dissolution rate depend on the solubility of the drug. Lower solubility of the drug gives slower dissolution rates and hence the diffusion front can overlap more easily with the erosion front, which yields erosion - controlled drug release. On the other hand, large solubility of the drug will give diffusion - controlled drug release (Bettini, R. et al. 2001).

3.2.2 Parameters controlling the release

The drug release from hydrophilic matrix tablets has been found to vary with the polymer parameters, the composition of the formulation, and the process parameters.

3.2.2.1 Polymer Viscosity and hydrophilicity

Examples of important polymer - related parameters with significant influence

on drug release are the viscosity and the hydrophilicity of the polymer, where polymers of larger viscosity grades give lower release rates and longer durations of the release (Gao, P., and Meury, R. H. 1996) and an increased hydrophilicity gives larger swelling and faster drug release, which was found by comparing different degrees of substitution of HPMC (Mitchell, K. et al.1993).

3.2.2.2 Formulation Composition

The drug release rate also depends on the composition of the formulation. When components with high water solubility, such as lactose, are included in the matrix, the drug release increases, which can be seen as a dilution of the gel – forming material (Levina, M. , and Rajabi - Siahboomi , A. R. 2004). Similarly, an increased amount of a soluble active substance also increases the release rate of drugs, probably also due to the corresponding decrease of the relative amount of hydrophilic polymer (Ford, J. L. et al.1985).

The size and shape of the tablet also influence drug release, and the release rate increases as the area - to -volume ratio increases (Reynolds, T. D. et al. 2002).

3.2.2.3 Polymer particle size

The influence of particle size on the drug release rate has also been investigated. The size of polymer particles seems to have low influence on drug release when there is enough gelling polymer available to quickly form a coherent gel layer. In contrast, at low amounts of hydrophilic matrix polymer, gel formation may be too slow, which makes polymer particle size important. In this case, the matrix may disintegrate before it develops a coherent gel layer (Velasco, M. V. et al.1999).

3.2.2.4 Drug particle size

The effect of drug particle size on the drug release rate depends on the solubility of the substance. Varying the particle size of drugs with high solubility seems to have little influence, whereas the release rate may depend on the particle sizes of drugs with moderate solubility (Ford, J. L.et al 1985).

3.2.2.5 Process effect

The effects of process parameters on drug release have been discussed in the literature. Different granulation technologies, such as dry granulation or wet granulation (which includes fluid bed granulation), have been used. Also direct compression has been used for production of hydrophilic matrix tablets (Velasco, M. V. et al.1999). The effects on the choice of production steps may be critical when the relative fraction of the polymers is low in the formulations. The effect of the compaction pressure on drug release has also been studied. Several authors (Liu, C. H. et al 1995) (Ford, J. L. et al 1985) have found that, while the compaction pressure has a significant effect on the tensile strength of the tablets, it has a minimal influence on drug release.

This can be due to the fact that, when a coherent gel layer is formed, only the parameters governing the performance of this gel layer are important, and since parameters such as porosity do not affect the gel layer, they are of low importance for the drug release rate.

3.2.3 Manufacturing of Hydrophilic Matrix Tablets

The traditional way of producing hydrophilic matrix tablets resembles the production of the core for membrane - coated tablets and insoluble matrix tablets. It includes a mixing step, possibly a granulation step, a compaction step, and sometimes a coating step. However, one large difference between the production of insoluble and soluble matrix systems is notable;

the latter matrix type has strong interactions with water, which complicates the production steps when water is present (Shah, N. H. et al 1996).

Therefore, for hydrophilic matrix systems with large fractions of hydrophilic polymers, traditional wet granulation with water as granulation liquid may cause problems with formation of hard lumps (Shah, N. H. et al.1996). To avoid this problem, a new technique using foam granulation has been suggested (Keary, C. M., and Sheskey, P. J. 2004). During granulation, the foams will flow on the top of already foam - wetted particles, which may lead to superior distribution of the granulation liquid. An alternative wet granulation method is to use organic solvents such as ethanol as granulation liquid (Cao, Q - R. et al 2005).

However, even if the production of granules with good compaction properties can be maintained in this way, it may be an advantage to consider the environmental aspects before choosing organic solvents as granulation liquid. Another alternative to wet granulation is to use dry granulation technologies such as roller compaction. Although this technique has several advantages compared to traditional wet granulation with water, it may result in lower tensile strengths of the tablets (Sheskey, P. J., and Williams, D. M.1996). An alternative to granulation technologies is direct compression. This can be done by purchasing special direct - compression qualities of the hydrophilic polymers. A drawback that always arises in relation to direct compression is the difficulty to achieve content uniformity of the tablets, a problem that increases with decreasing doses of the active drug. Therefore, special care should be taken with regard to formulations with low doses of active substance when direct compaction is used.

To be successfully used in controlled drug delivery formulations, a polymer must be chemically inert and free of leachable impurities. It must also have an appropriate physical structure, with minimal undesired aging, and be readily processable. Polymers used to

formulate controlled release devices are necessarily biocompatible, and ideally biodegradable. Polymers can be classified into:

1-**Synthetic polymers**: The literature gives examples of synthetic polymers such as the Eudragit® (RöhmPharma, Weiterstadt.); range of polyacrylate methacrylate copolymers. Other synthetic polymer is Carbomer.

2-**Natural polymers**: Naturally occurring polymers and biopolymers are also applied in the manufacturing of controlled release devices. Biopolymers are produced through variety of mechanisms. They can be derived from microbial systems, extracted from higher organisms such as plants, the most common type used for hydrophilic matrix systems are Cellulose derivatives such as HPMC, methylcellulose, hydroxyethylcellulose, Hydroxypropyl cellulose and sodium carboxymethylcellulose.

3.3 Membrane - coated Oral Extended Release

3.3.1 Multi-particulate systems:

Although it can be single unit (tablet) or multi-particulate system, it is more common and applicable with the multi-particulate systems.

Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of several spherical particles with diameter of 0.05-2.00 mm. Thus multi-particulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet or encapsulated or compressed into a tablet. Multi-particulates are discrete particles that make up a multiple unit system.

3.3.2 Why multi-particulate systems

Although their manufacture and design is more complex in comparison to single-unit dosage forms, multi-particulate systems offer a magnitude of differing interesting options and advantages to accomplish unique product characteristics and in particular specific drug release patterns. In contrast to single-unit forms, which retain their structure in the digestive tract, the multi-particular preparations consist of numerous sub-units, which disperse after administration. Each single sub-unit acts as an individual modified release entity. As a consequence of this property, the multiple-unit approach offers certain advantages for a modified release dosage form over single-unit, monolithic, preparations (NS Dey, S. Majumdar and MEB Rao, 2008):

- Reduced variability of the gastric emptying
- As a consequence lower dependency on the nutrition state
- Minimized risk of high local drug concentrations within the GI-tract
- Reduced risk of sudden dose dumping
- Lower intra- and inter-individual variability of absorption of the drug substance into the systemic circulation
- They can also be used to provide different release profile at the same or different sites in the gastrointestinal tract
- Chemically incompatible products can be formulated into pellets and delivered in a single dosage form by encapsulating them
- Multi-particulate systems show better reproducible pharmacokinetic behavior than conventional (monolithic) formulations. After disintegration which occurs within a few minutes often even within seconds, the individual subunit particles pass rapidly through the GI tract. If these subunits have diameters of less than 2mm, they are able to leave the stomach continuously, even if the pylorus is closed.

Spherical particles not only offer flow but also offer high degree of flexibility in the design and development of oral dosage form like suspension, sachet, tablet and capsule.

3.3.3 Multi-particulates preparation methods:

The first step in the production of membrane - coated systems is to prepare the drug reservoir, the core, of the system. Multi-particulates may be prepared by several methods. Different methods require different processing conditions and produce multi-particulates of distinct qualities. The production of cores for multiple - unit systems (often termed pellets) is more sophisticated than monolithic system and may be performed in different ways. The most common used methods for manufacturing the core pellets are:

3.3.3.1 Extrusion and Spheronization:

In this case the active substance is one of the core ingredients, and it is usually of high dose. The process of wet extrusion, followed by spheronization, is used to produce a wide variety of controlled release drugs. These solid dosage forms are mostly in the form of tablets or capsules containing high levels of an Active Pharmaceutical Ingredient (API).

Advantages and product characteristics for extrusion and spheronization include:

- Dense pellets
- Smooth coatable pellets
- Narrow particle size distributions, and
- High yield and flowability.

The wet extrusion process can be batch or continuous operation and consists of the following steps:

Mixing: The pre-mixed dry ingredients, mostly composed of the API and microcrystalline cellulose, are wetted with water or organic solvent and mixed in a high shear granulator or double planetary mixer to form a homogeneous wet mass suitable for wet extrusion.

Extrusion: The wet mass is metered by a special feeder into the extruder where it is continuously formed into cylindrical extrudates of uniform shape and size.

Spheronization: The wet extrudates are placed in a spheronizer where a gridded, fast spinning disc, breaks them into smaller particles and rounds them to form spheres.

In general, the core will include active substance together with the filler materials. Classical filler materials are lactose and microcrystalline cellulose, but also other materials such as dextrose, mannitol, sorbitol, and sucrose can be used. However, it should be remembered that the dissolution of the filler material might influence the osmotic pressure.

3.3.3.2 Mini-tablets

In this case also the drug is one of the core ingredients. The process is a normal tableting process, including the following steps:

Mixing: the ingredients including the active are either directly mixed or granulated with proper solvent and binder then dried, sized and finally lubricated.

Compression: the pre-mixed powder is compressed into small round tablets of diameter less th an 2 mm, using multi-tip punches of small diameter.

3.3.3.3 Inert Cores (nonpareil beads)

Non-Pareil Seeds are specially designed, ready-made, spherical particles of uniform diameter within different grades. They are white, uniform granules that are practically inert and odorless. Non-Pareil Seeds are available in different standard sieve sizes. They may be made of different inert materials, such as sucrose, starch or microcrystalline cellulose.

In this case, the manufacturing procedure is more sophisticated and challenging, the drug should be incorporated to the placebo pellets by layering in the form of suspension or solution with a binding polymer. This requires high skills and special machinery and long processing time, especially if high dose is required.

3.3.4 Principles of Formulation and Release Mechanisms

The purpose of designing multi-particulate dosage form is to develop a reliable formulation that has all the advantages of a single unit formulations and yet devoid of the danger of alteration in drug release profile and formulation behavior due to unit to unit variation, change in gastro –luminal pH and enzyme population. An accepted view is that multi-particulate systems perform better in vivo than single unit system, as they spread out through the length of the intestine cause less irritation, enjoy a slower transit through the colon and give a more reproducible drug release.

One way to protect the drug from being directly released is to coat the system with an insoluble film. The drug is suspended or dissolved in a reservoir system which can consist of monolithic or multiple - unit systems. The release controlling films surrounding the reservoir will be insoluble and thus give the system extended drug release properties.

In CR reservoir systems, a membrane surrounds a reservoir of the drug, also called the core of the system. The membrane controls the drug release and the driving force is the difference in chemical potential over the membrane, which can be correlated with a concentration gradient over the membrane. The transport of the drug through the CR membranes can be divided into three different mechanisms (Savastano, L. et al.1995):

- Diffusion through the membrane
- Diffusion through pores and cracks in the membrane
- Osmotic transport through pores, cracks, or drilled holes

The overall drug release process for common membrane - coated systems has been shown to pass through three different time periods (Figure 2) (Ragnarsson, G. et al.1992). During the initial period, the amount of released drug will be low. The water penetrates the Membrane and at the same time starts to dissolve the material in existing pores, consisting of water - soluble sugars, salt, or polymers. The water that has penetrated the membrane and reached the

core starts to dissolve the active substance in the reservoir (Ragnarsson, G., and Johansson, M. O.1988). The concentration of the active drug increases continuously until its saturation concentration has been reached and equilibrium between the solid material and saturated solution inside the membrane has developed. The osmotic pressure in the reservoir will depend on the concentrations of all dissolved species inside the membrane, and an increase of the osmotic pressure may lead to membrane rupture. After an initial lag period, the number of cracks and pores becomes constant, and the osmotic pressure and the concentration of dissolved species in the reservoir and in the membrane reach their steady - state levels. When these parameters, which are the driving forces for the drug release, are constant, the drug release rate will also be constant. Therefore, a second period with time - independent drug release rate will occur when the solid drug material inside the membrane is completely dissolved and the concentration of the dissolved drug decreases, a final period with declining release rate will be entered. Ragnarsson et al.1987 have shown that the solid material disappears earlier as the drug solubility increases and that the third stage with time - dependent and decreasing release rate appears earlier compared to drugs with lower solubility.

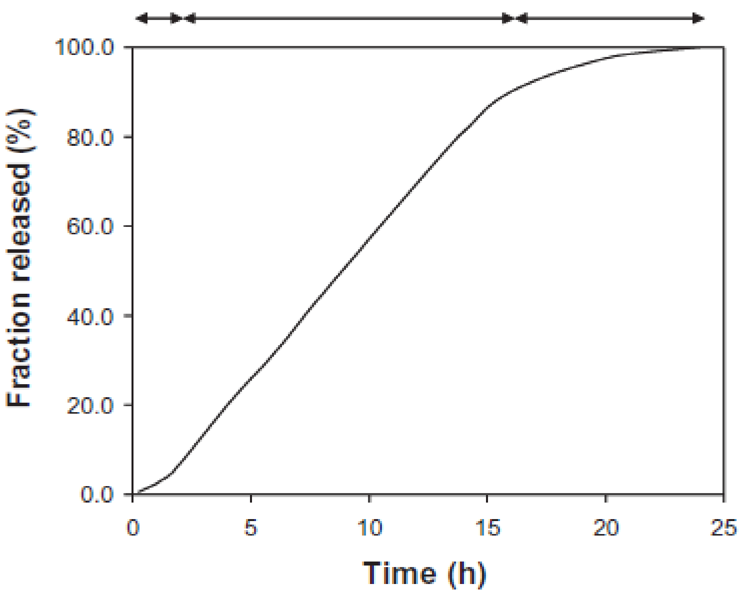


FIGURE 2 Release from membrane - coated reservoir system, where the three different stages are depicted (initial lag period, “steady - state” period, and final depletion period).

3.3.5 Osmotic pump system:

One special type of CR formulation based on coated reservoir systems is the so - called osmotic - controlled oral drug delivery system or osmotic pump. Pure osmotic systems have semipermeable membranes; that is, water can permeate the membrane but not other substances. These semipermeable membranes can be made of, for example, cellulose acetate (Edgar, K. J., Buchanan, C. M. 2001), and for such formulations the dominating release mechanism is the osmotic pressure. The oldest formulation based on osmotic release was OROS from Alza Corporation (Theeuwes, F.1975). In order to achieve drug release through the semipermeable membrane, a laser hole was drilled, but today many osmotic formulations instead use pores filled with water - soluble materials.

Some advantages with osmotic pumps compared to other CR formulations such as hydrophilic matrix systems are:

(i) The time - independent drug release (often mentioned as zero – order release)

(ii) The superior in vivo – in vitro correlation which facilitates further formulation development, and

(iii) Less variation between fasted and fed states.

Potential drawbacks may be high initial development costs and the need for special equipment associated with laser drilling technology (Shayne cox gad, 2008).

3.3.6 Manufacturing of Oral (Membrane – Coated) Systems:

3.3.6.1 Coating Equipment:

Equipment used in film coating can be classified into three general categories:

Solid pans, perforated pans, and fluid-bed processors, the latter two only are suitable for film coating. These systems are used to contain the materials being coated and provide an environment for the coating to dry. They should also provide a means to ensure that an equal amount of coating material is applied evenly to each particle. The delivery system conveys

the coating material to the coating equipment in a controlled and desired fashion. Support equipment contributes to automation and includes the control systems. The available coating equipment systems vary from simple air handlers and manual process control to automated processes and dew point control. Coating is an old processing technique and has been utilized for centuries. Early coatings were applied to products by rolling the product in a mass of wet coating material and continuing the rolling until it was dry. The rolling action distributed the coating uniformly over the surface of the object being coated as it was slowly drying. Heat was sometimes applied at various stages during the process to accelerate the drying. The process was typically carried out in a shallow pan hung from the ceiling over an open fire. Needless to say, coating was a slow process and achieved inconsistent results. Recently, the perforated pans and fluid bed equipment make the process easier and faster.

3.3.6.1.1 Perforated Pans:

For coating of larger units, such as tablets or capsules, a rotating drum is often used.

This type of equipment contains a perforated pan that rotates and thus mixes the bed of units. At the same time, a coating liquid is applied to the moving units by means of a spray gun, where the mixing of the units ensures uniform coverage of the coating. The film coating is dried by blowing a stream of hot air onto the surface of the tablets. For all types of coating processes, there are many parameters, such as the temperature and relative humidity of the inlet air, drum rotation speed, spraying rate, and droplet size of the coating liquid, that have to be adjusted in order to produce good coated films.

3.3.6.1.2 Fluid Bed:

For coating smaller units, such as pellets, the fluid bed coating technique is used. This is an attractive technique in which the starting material is placed in the coater and heated air is

blown through a base plate. This leads to vigorous mixing of the pellet units. By changing the pressure of the incoming air stream, the material becomes suspended in the air. This happens when the bed starts to fluidize and the bed will then have fluidized properties similar to the properties of ordinary liquids.

There are different designs of fluid bed as shown in figure 3: top spray coating, bottom spray coating (Wurster coating), or tangential coating. They differ with regard to placement of the spray guns. In top spray coating, the liquid is sprayed from the top of the equipment and the droplets hit the particles moving in opposite direction. In the bottom spray coating, the sprayed liquid drops and particles flow in the same direction; this avoids the problem of blocking of the spray guns that may occur in top spray equipment. In the Wurster process, the coating liquid is applied concurrently with the flow of the product. The Wurster system combines a partition (column) and an air distribution plate to organize the flow of particles in close proximity to the spray nozzle. Because the nozzle is immersed in the air flow in order to spray concurrently into the fluidized particles, the dispersion droplets travel only a short distance before impinging on the product. As a result, the film is applied more evenly. On the other hand, spray drying of the coating dispersion is minimal with this process.

In the more rarely tangential spray coating equipment the base plate rotates and the spray guns are spraying in a tangential direction to the spiral moving particles (Cole, G. et al 1995).

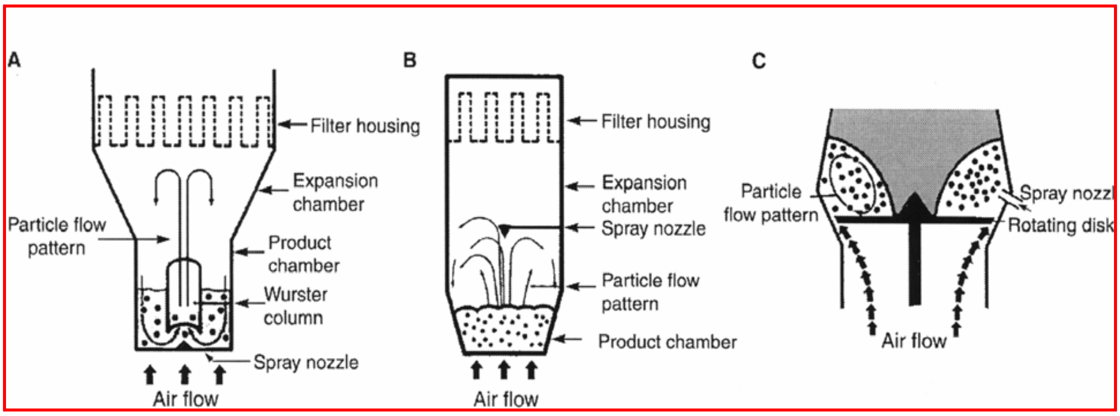


Figure 3: Schematic of a fluidized bed apparatus: (A) bottom spray with Wurster column insert; (B) top spray technique; (C) tangential spray technique (Felton, 2007).

3.3.6.2 Coating Process:

A critical parameter for obtaining films with desirable properties is the creation of coating droplets, a process often referred to as atomization, that is, when a bulk liquid is dispersed in air to form a spray or a mist. Atomization is done by letting pressurized air and bulk solution pass simultaneously through a nozzle (spray gun). The air divides the droplets into smaller units, but in spite of the name atomization, the droplets are dispersed not at atomic scale but rather in the Nano– to micrometer - scale range (Aulton, M. E., and Twitchell, A. M.1995). The mechanism for film formation depends on whether the polymer is dissolved or dispersed as small latex particles in the solution. For both technologies the film formation process starts with wetting and spreading of the coating droplets on the surface of the reservoir system. For the case with polymer dissolved in solution, the film formation mechanism continues with evaporation of the solvent. This leads to an increase of the polymer concentration, and at a certain limit the polymers precipitate and a coated film is formed. So, Formation of an acceptable layer of film on the substrate requires the following (James W. McGinity and Linda A. Felton, 2008):

- Formation of appropriate-size droplets
- Contact of these droplets with the substrate
- Spreading and coalescence of the droplets
- Evaporation of the solvent

3.3.6.3 Fluid bed Layering and Coating Process Variables

For a fluid bed coating, the following process variables need to be monitored and controlled to produce a product with consistent quality:

3.3.6.3.1 Spray rate

Spray rate is the rate of applying liquid coating solutions/suspensions to solid substrates in a fluid bed system. Many factors, such as the viscosity and tackiness of the coating liquid, the droplet size, and the drying capacity of the fluidized bed system, can limit the maximum spray rate. If the spray rate is too high, irreversible agglomeration can occur, which may result in batch failure. Therefore, the spray rate should be set conservatively for initial trials. For any coating process, a short coating time and a high quality film must be balanced.

3.3.6.3.2 Atomization air pressure

Atomization air pressure is an important key process parameter to control droplet size distribution and velocity. Optimal droplet size distribution and velocity are critical for an efficient process, which helps prevent over wetting and spray drying. Increasing the atomization air pressure will increase the volume and velocity of the air passing through the nozzle, thus affecting the spray pattern and reduce the droplet size. Too much atomization air pressure leads to spray drying, while too little atomization air pressure can result in agglomeration.

3.3.6.3.3 Inlet air temperature

Inlet temperature is the temperature of the heated air taken right before it enters the product container. For coating, the inlet temperature is set relatively low compared to drying. This is because a high inlet temperature can lead to film softening, which may result in agglomeration during coating. An optimal range needs to be defined for every coating system.

3.3.6.3.4 Inlet air volume

Fluidization pattern and the upward velocity of the particles in a fluidized bed system are determined by the inlet air volume. The upward movement of the particles should be properly controlled. If the air volume is too high, the particles can be trapped in the filter housing or

eroded if friable. If the air volume is too low, the particles may get over wetted when passing through the spray zone.

3.3.6.3.5 Inlet air humidity

Inlet air humidity is usually indicated by the dew point temperature, at which the air is saturated with moisture. With unconditioned air, the moisture carrying capacity of the air varies. The spray rate needs to be reduced if the inlet air humidity is high, otherwise over wetting may be an issue. High inlet air humidity also makes it difficult to remove residual moisture in films. Extra moisture remaining in the product may cause stability problem. The spray rate needs to be increased if the inlet air humidity is low, otherwise spray drying may occur. For a functional coating process, dew point control is even more important, because it is related to the moisture remaining in the film. Moisture in a film can often function as a plasticizer, and thus change the drug release profile during storage. With conditioned air, the dew point of the inlet air is consistent for each batch, which allows a reproducible drying rate and better film quality. The combination of inlet temperature, air volume, and inlet air humidity determines the drying capacity of a fluid bed system, thus the maximum output of the system.

3.3.6.3.6 Product and exhaust temperature

Product and exhaust temperatures are two commonly monitored parameters. The product temperature is more sensitive than exhaust temperature. The inlet temperature and inlet air volume have a positive impact, while the spray rate has a negative impact on the product temperature. In a coating process, if the product temperature is lower than the minimum film-forming temperature, it will result in the formation of poorly coalesced film and faster drug release rate. If the temperature is too high, agglomeration may occur.

4. Coating materials for CR products & pseudo-latex dispersions:

The choice of film - forming materials and film - coating techniques is critical for the drug release rate. The CR membrane should remain intact during the release, which implies that it should not dissolve or erode.

As film - forming material, water - insoluble substituted cellulose derivatives such as ethyl cellulose (EC) have been widely used, as well as synthetic polymers such as methyl acrylates and polyvinyl acetate. As all of these polymers are water insoluble, their coating solutions are organic, which is not favorable.

Environmental and economic factors have caused an ambitious shift from organic solvent–based to water-based film coatings for pharmaceutical dosage forms. However, the development and introduction of latex and pseudo-latex materials as well as improvements in equipment design have broadened the spectrum of aqueous coating. With correctly selected equipment and processing conditions, it is now possible to apply water-based films to small particles without agglomeration or to tablets containing super-disintegrants without core penetration and dissolution of the tablet surface. Aqueous pseudo-latex colloidal polymer dispersions offer several advantages over polymers dissolved in organic solvents, including (James W. McGinity and Linda A. Felton, 2008):

- Lower spraying viscosities,
- Higher solids loading,
- Higher spray rates,
- No solvent environmental, toxicity, or flammability issues.
- Reduced energy requirements relative to aqueous polymer solutions.

Film formation from pseudo-latex aqueous dispersion has four steps (James W. McGinity and Linda A. Felton, 2008) (figure 4):

1. Ordering and close packing of the particles due to water evaporation to give a face-centered cubic construction.
2. Deformation and filling the voids left by the removal of water to give a foam structure.
3. Coalescence or fusion of the particles due to fragmentation of the hydrophilic layers between particle cores, leading to phase inversion where the remaining water is no longer the continuous phase; and
4. Polymer interpenetration between cores, forming a continuous polymer matrix and erasing the original particle identity.

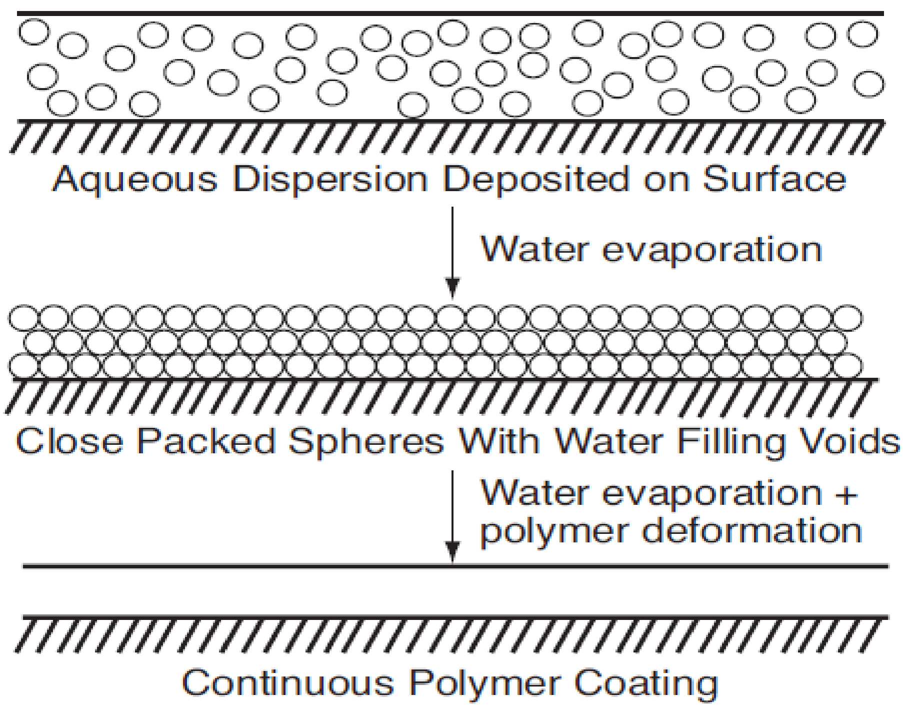


Figure 4 Film formation from a pseudo-latex dispersion (Onions A. 1986)

5. Pseudo-latex Aqueous Dispersions for CR Coating:

Polymers for aqueous film coating may be grouped into cellulose ether derivatives, Acrylic resins and polyvinyl acetate.

From celluloses, the commonly used polymer is Ethyl cellulose. Commercially available Ethyl cellulose dispersions are (Aquacoat® ECD, FMC Corp., Philadelphia, PA) and (Surelease®, Colorcon, Inc., West Point, PA).

Aquacoat ECD is a 30% w/w aqueous dispersion of Ethyl Cellulose with sodium lauryl sulfate and cetyl alcohol as stabilizers. Surelease is a 25% w/w aqueous dispersion of EC as the rate controlling polymer plasticized with ammonium oleate and dibutyl sebacate.

The acrylic resin derivatives are available as 30% w/w poly(metha) acrylate lattices (Eudragit® RL 30 D, RS 30 D, NE 30 D, NE 40 D, L 30 D-55, and FS 30 D, Rhom Pharma, Darmstadt, Germany). The ammonium groups in Eudragit RL 30 D and Eudragit RS 30 D are present as salts and make the polymers permeable. Eudragit RL 30 D forms a readily permeable film, whereas Eudragit RS 30 D films are sparingly permeable. By varying the composition of a polymer blend of Eudragit RS 30 D and RL 30 D, the permeability of a combination film can be controlled. In addition, the permeability of Eudragit RL/RS films is independent of the pH. Eudragit NE 30 D is quite permeable and is generally used in conventional dosage forms. Eudragit NE 40 D is aqueous dispersion identical to Eudragit NE 30 D with 40% solid particles.

Other valuable aqueous-coating agents commercially available from BASF include the Kollicoat® family of products. For extended release purposes they have Kollicoat SR 30D which is a 30% aqueous dispersion of polyvinyl acetate stabilized with povidone and sodium lauryl sulfate for sustained release coating and taste masking.

6. Active Layering Process:

Ideal substrates for coating applications should be dense, have spherical and smooth surfaces with minimal porosity, and have narrow particle size distribution. The substrates should be hard enough with good attrition strengths to avoid ruptures during the coating process and sustain fluidization, stable at elevated temperature and moisture level, and non-cohesive. Pellets, granules, and mini tablets are examples of substrates used in multi-particulate systems. Many different techniques, such as extrusion spheronization, drug layering, granulation, and compaction, can be used to make substrates for subsequent coating. Selection of a technique should be based on the physical–chemical characterization of the drug substance.

Pellets are good substrates for layering and coating because they have spherical shape, suitable particle size/density, and smooth surface. Drugs are incorporated into pellets either as drug layers or as matrix systems. For active layering, different inert cores, such as sugar spheres (nonpareil) and microcrystalline cellulose spheres (Cellets), are commercially available. For matrix systems, pellets can be prepared by extrusion spheronization or rotary fluid bed pelletization process.

Active ingredients can be layered onto inert cores in two ways (Hong Wen, and Kinam Park, 2010):

1. Spray a solution or suspension containing both drugs and binding agents onto inert cores.
2. Layer drug powders onto inert cores directly.

Solution layering is a good choice for drugs with reasonable solubility and viscosity. Suspension layering is more flexible due to its low viscosity and its capability for high drug loading. For both approaches, dissolving drug substances in liquids and spray layering onto pellets may cause transformation of the drug polymorphic state. Crystalline drugs may convert to a different crystalline state or even the amorphous state. This will change drug

release profile on storage and cause stability concern. For both suspension layering and dry powder layering, it is important to control the particle size of the drug substance, which should be sufficiently small compared to the inert cores, to ensure good adhesion and uniform coating. After the layering process, the drug layered particles maintain spherical shape and a narrow particle size distribution (Hong Wen, and Kinam Park, 2010).

It is critical to control the size and size distribution of pellets prior to the coating process. The size of pellets has an impact on pellet's fluidization pattern and velocity, thus affecting coating thickness. Larger or heavier pellets, with a longer residence time in the spray zone, form a thicker film and exhibit a much slower release rate than smaller or lighter pellets (Wesdyk R et al, 1990). Particles less than 100 µm are very cohesive, thus leading to agglomeration and poor coating. Meanwhile, the particle surface area is directly related to the particle size, whereas smaller particles have larger overall surface area and require a higher amount of coating than larger particles for the same release profile. For the same amount of coating material, smaller particles or higher surface areas lead to thinner films, thus a faster release.

Therefore, both a desirable pellet size and a narrow particle size distribution are important to achieve a tight and reproducible release profile (Hong Wen, and Kinam Park, 2010). Particles with a smooth surface are preferred over a rough surface. The rough surface can significantly increase the surface area and the coating materials trapped in the pores cannot function as a release barrier Particles with a high friability tend to break and create fines during fluidization and lead to uncontrolled release of drugs (Chopra R et al, 2002).

7. Objectives and hypothesis of the study

7.1. Hypothesis

A high dose, highly water soluble drug can be formulated into a controlled release multiparticulate dosage form using active layering technology.

7.2. Objective

To formulate the high dose, highly water soluble model drug Diltiazem Hydrochloride into a controlled – release, multiparticulate dosage form using active layering technique in a Wurster – column, bottom-spray, fluid bed processor.

7.3. Specific Aims

1. To load the model drug, Diltiazem HCl, onto ready-made sugar spheres by active layering technique using a Wurster – column, bottom-spray, fluid bed processor.
2. To study the effect of the drug-loading formulation on the efficiency of the process and drug release from the drug loaded spheres.
3. To coat the drug loaded spheres with another semi-permeable, controlled-release membrane coating layer using the same facility.
4. To study the effect of the controlled release coating formulation on the efficiency of the process and drug release from controlled release spheres.
5. To study the effect of curing on drug release from controlled release spheres.

6. Importance of the study

Traditionally, sustained release dosage forms of both types; matrix or membrane systems were used to be formulated as tablets, which can be prepared by conventional pressing and coating machines. This type of dosage form is easily copied and marketed by generic manufacturers, this results in increased number of competitors in the market and reduced profits of the brand companies that develops and introduces the drug. This has led the brand companies to invent new more complicated technologies for the manufacturing of their controlled or delayed release dosage forms.

Multi-particulate systems, besides having the drug delivery related advantages mentioned in previous sections, have served a very big advantage to the brand companies by reducing the number of competitors who can use the same or similar technology.

Some of factors behind this reduction in the numbers of able competitors are,

(i) the capital investment associated with the procurement of processors,

(ii) the need for skilled and qualified operators of the processors,

(iii) the relatively limited knowledge and experience with the technologies which is a very important factor considering the fact that many formulation and process variables interact to affect the quality of the coated multiparticulate products.

In spite of all these factors, many generic pharmaceutical manufacturers are getting into the multiparticulate dosage forms area simply because attempts to compete with multiparticulate based products using conventional single-unit ones are usually unsuccessful as single and multiple unit dosage forms are usually not bioequivalent even if the in vitro dissolution profiles are a match because of the huge difference in their biopharmaceutical behavior.

The brand product of Diltiazem hydrochloride (Cardizem CD) has been manufactured using two different techniques for each process; first is extrusion-spheronization for drug incorporation into the dosage form or dry powder layering, and spray coating for application

of release controlling membrane (US patent 5,470,584). Such a process causes the production to be more expensive because the need for more than one facility for the manufacturing process. In our work we attempted to perform the whole manufacturing process using the same facility by active layering of Diltiazem HCl prepare the particles which are later coated by the rate controlling polymer instead of using extrusion-spheronization. Besides reducing the processing space requirements, time and cost, the proposed procedure is expected to have the advantage of reduced potential for cross – contamination in the manufacturing plant.

Experimental Section:

1. Materials:

1.1 Active Material (Diltiazem HCl)

Supplier: Transo-Pharm (India)

Diltiazem hydrochloride is a calcium ion cellular influx inhibitor (slow channel blocker or calcium antagonist). Chemically, Diltiazem hydrochloride is *cis*-(+)-[2-(2-dimethylaminoethyl)-5-(4-methoxyphenyl) -3-oxo-6-thia-2-azabicyclo[5.4.0]undeca-7,9, 11-trien-4-yl]ethanoate. (Molecular weight 450.99 g/mole). The chemical structure is shown in figure (5):

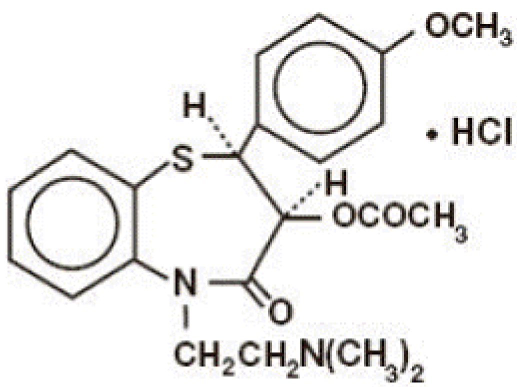


Figure (5) structural formula of Diltiazem HCl

Diltiazem HCl is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform with an aqueous solubility of greater than 590 mg/ml (at 37 degrees C).

Pharmacokinetics and Metabolism

Diltiazem HCl is well absorbed from the gastrointestinal tract, and is subject to an extensive first-pass effect. When given as an immediate release oral formulation, the absolute bioavailability (compared to intravenous administration) of diltiazem HCl is approximately

40%. Diltiazem HCl undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine.

The plasma elimination half-life of Diltiazem HCl is approximately 3.0 to 4.5 h. The apparent elimination half-life after single or multiple dosing of sustained release pellets is 4 to 9.5 hours (mean 6.5 hours).

Because of its short biological half-life (3.5 h) and low oral bioavailability (40%) due to hepatic metabolism leading to high frequency drug dosing, the continuous delivery of Diltiazem HCl is required.

1.2 Excipients:

1.2.1 Starter Inert Pellets:

Surespheres from colorcon were used; they are white spherical granules with sweet taste, soluble in water with Particle size of 500 - 600 µm. They are composed of sucrose (up to 92%) and maize starch. These drug layering substrates, are defined as small, free flowing, spherical pellets manufactured by the agglomeration of fine powders.

Required features are narrow particle size distribution, low friability, high mechanical strength, Smooth surface and spherical shape.

1.2.2 Kollicoat IR (KIR):

Manufactured by BASF chemicals, it is a polyvinyl alcohol – polyethylene glycol graft copolymer is a new pharmaceutical excipient that was specially developed as a coating polymer for instant release tablets.

The polymer consists of 75% polyvinyl alcohol units and 25% polyethylene glycol units. The product also contains approx. 0.3% colloidal silica to improve its flow properties.

As a result of its structure, the polymer dissolves very readily in acidic, neutral and alkaline aqueous media. Such aqueous solutions have a comparatively low viscosity.

It is a free flow powder with Molecular weight of 45000 Daltons and Melting point of 209°c. For solution of 20% the pH is 6.7, and the Viscosity is 115 mPas.

Solutions of Kollicoat® IR with concentrations of up to 40% can be prepared in water and aqueous systems, e. g. weak acids or alkalis. Solutions of up to 25% can be prepared in 1:1 ethanol-water mixture. Its solubility in non-polar solvents is low, and it can only be dispersed. When the water has evaporated from polymer aqueous solution, a clear, colorless, flexible film remains. Kollicoat® IR films are not tacky, have a high pigment binding capacity and can readily be printed. Kollicoat® IR has a much higher elongation at break value than cellulose derivatives (BASF technical information site).

Structural formula

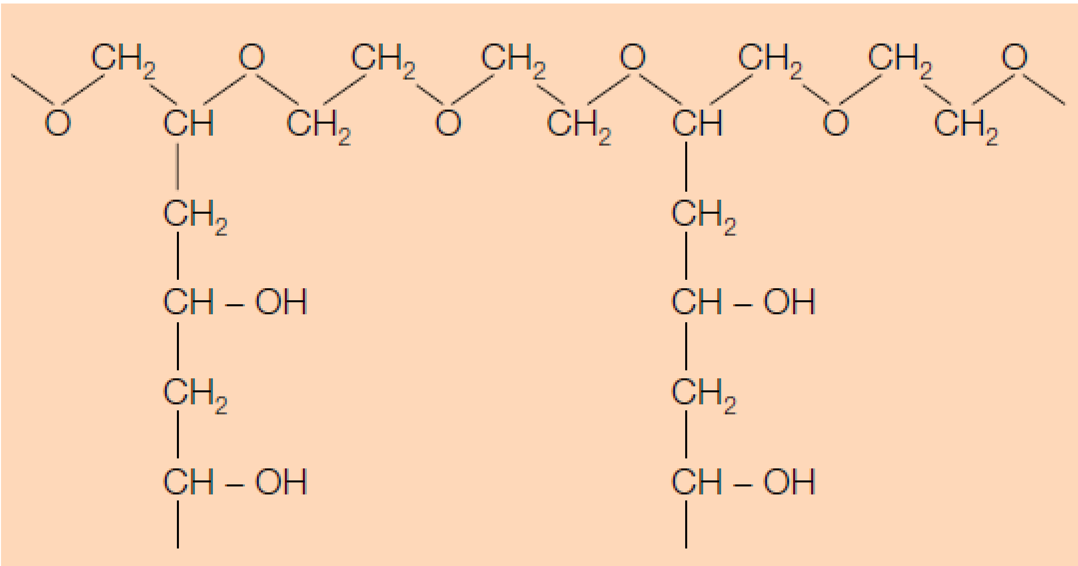


Figure 6: Kollicoat IR structure

1.2.3 Kollicoat SR 30 D:

Manufactured by BASF chemicals, it is a polyvinyl acetate dispersion stabilized with povidone and sodium lauryl sulfate. The dispersion is suitable for the manufacture of pH independent sustained-release formulations. The dispersion can also be used for taste masking. The dispersion consists of about 27% polyvinyl acetate, 2.7% povidone and 0.3% sodium lauryl sulfate. The low viscosity product has a weak characteristic odor and a milky white or slightly yellowish appearance.

The minimum film-forming temperature (MFT) of the pure dispersion is 18 °C. It can be lowered by adding plasticizers. The recommended plasticizer content is 0 – 10% with reference to the dried polymer substance.

Kollicoat SR 30 D is miscible with water in any ratio while retaining its milky-white appearance. Mixing the product with ethanol or isopropyl alcohol in a (1:5) ratio produces a slightly turbid and somewhat viscous solution; a solution in acetone is more turbid. When organic solvents are added, the polymer precipitates at first, but then dissolves when further solvent is added. Kollicoat SR 30 D is insoluble in dilute alkaline or acidic solutions.

It meets current Poly (Vinyl Acetate) Dispersion 30 Per Cent Ph. Eur. monograph. A draft USP/NF monograph entitled „Polyvinyl Acetate Dispersion was published in Pharmacopeial Forum 35 (1) January 2009 (BASF technical information site).

Structural formula

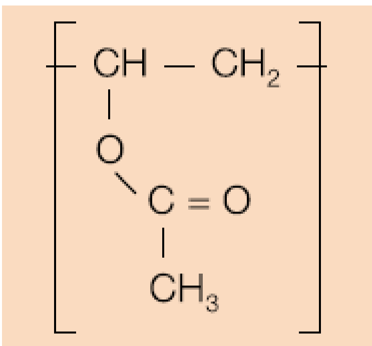


Figure 7: Kollicoat SR structure

2. Equipment:

(i) Propeller mixer (IKA)

(ii) Dissolution tester (PharmaTest, PTWS1200), Germany

(iii) Spectrophotometer (THERMO: Evolution 300 BB)

(iv) UNI-Glatt fluid bed coater (Wurster), Glatt, Germany

(v) Static oven (HERAEUS, B 6200), Germany

(vi) Stability chamber. (HERAEUS, B 6200), Germany

(vii) Surface measurement systems (DVS Advantage)

(viii) DSC TA (Q2000)

(ix) Dissolution tester (Vankel, 10-1700E) with autosampler.

3. Methods

3.1. Drug layering

The purpose of this stage was to apply the DTZ on neutral sugar spheres with the aid of a polymer (Kollicoat IR) to enhance binding of the drug to the spheres.

Since DTZ is highly water- soluble, it was dissolved along with the polymer in water and applied together to the spheres in the form of solution.

Layering process was performed using Wurster column technique by spraying the DTZ-KIR solution on the sugar spheres.

To optimize the formulation, two different ratio of the drug-polymer solution were performed to get different loading weights. The following are the trials that have been performed:

Table 1: Active layering trials.

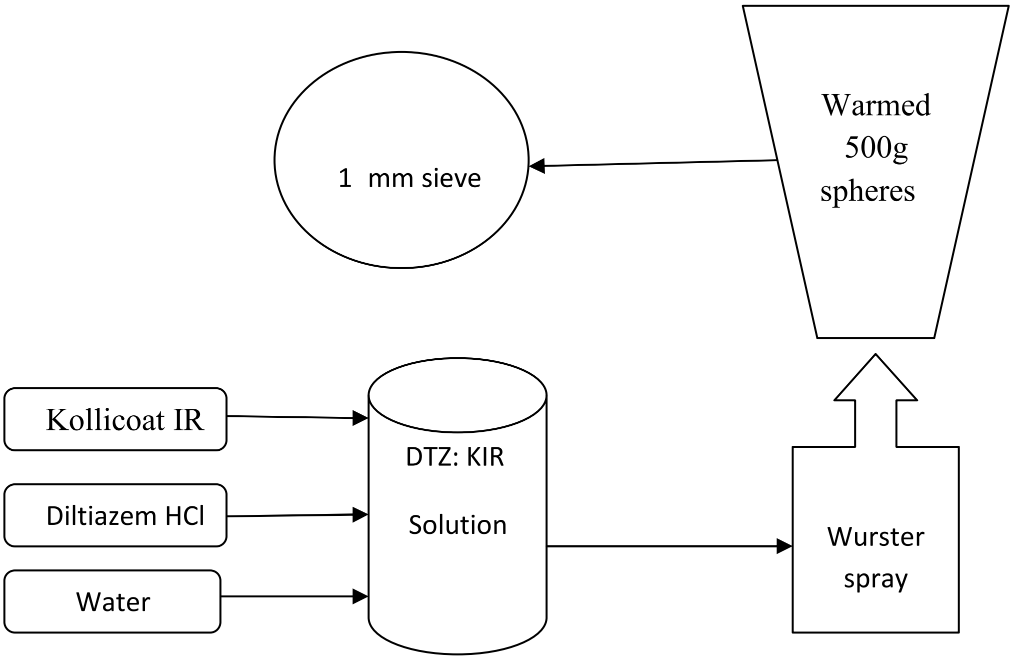
DTZ:KIR (w:w) Ratio	Trial No.	Target Loading (weight gain)
5 : 1	1	30
	3	60
	5	120
5 : 2	2	30
	4	60
	6	120

The solutions for all trials were prepared according to the following compositions, and spraying continued until the target weight gain was achieved.

Table 2: Compositions of drug layering solutions

composition	5:1 Trials	5:2 Trials
DiltiazemHCl	25	25
Kollicoat IR	5	10
Water q.s to	100 ml	100 ml

The manufacturing procedure is shown in the following flow diagram.



The manufacturing conditions in the fluid bed processor were monitored throughout the process and are presented in Table 3.

Table 3: Drug layering process parameters

Inlet air temperature	50-55°c
Outlet air temperature	40°c
Atomizing pressure	2 bar
Air flap	25-30
Pump speed	9-10 rpm
Spraying rate	220 g/hr.

3.2. Appearance:

Pellets in all trials were tested visually for uniformity and freedom of agglomerates.

3.3. Analytical Method:

The concentration of DTZ in assay and dissolution samples was determined through measurement of UV spectrophotometric absorbance at a wave length of 237 nm and the use of linear calibration plots.

Linearity:

The analytical procedure was evaluated in terms of linearity by preparing solutions of different concentrations of DTZ in water in the range of 6 mg% to 133 mg % and measurement of their absorption at λ=237nm.

3.4. Placebo Interference and selectivity:

All excipients were mixed with DTZ in ratios similar to the final formulation composition and dissolved/dispersed in water using sonication for two minutes. A sample was then withdrawn from the prepared dispersion and filtered through a 0.45 µm nylon filter before its absorbance was measured at 237nm.

3.5. Weight gain & Assay:

Actual weight gain was calculated by comparing the resulting actual weight after coating to the theoretical weight supposed to be achieved in each trial, multiplied with 100%, assuming that the loss is equal from the core pellets and the spraying solution.

Assay:

Drug layered pellets were ground using mortar and pestle and an accurately weighed amount of the milled pellets equivalent to about 33.33mg of DTZ was taken and added to about 50 mL of water in a 250ml volumetric flask and sonicated for 10 minutes before completing up to volume using water. A 6 mL portion of the above solution was withdrawn volumetrically and diluted with water in 50 mL volumetric flask.

The absorbance of the final solution was measured at a wavelength of 237nm and the concentration of DTZ was calculated using linear calibration curve.

The assay procedure was performed in triplicates and results were expressed as mean and standard deviation.

3.6. Dissolution of active – layered pellets

Dissolution studies were conducted in a USP dissolution apparatus II (PharmaTest, PTWS1200) over a 60 minutes period using 900 ml of deionized water as dissolution medium. The stirring rate and temperature were adjusted to 75 rpm and 37±0.5^{o}C, respectively. At predetermined time intervals, 6 mL samples were withdrawn for analysis and immediately replaced with an equal volume of fresh medium maintained at the same temperature. The sample was diluted with water to 50ml in volumetric flask and a portion of the resultant solution was filtered using 0.45µm syringe filters before the absorbance of DTZ was measured at 237 nm (THERMO: Evolution 300 BB). DTZ concentration was calculated from linear calibration plots. The dissolution tests were performed in triplicates and the mean values as well as standard deviations were calculated.

In all trials layered pellets were filled into size zero colorless capsules according to its filling weight taking into consideration the assay results.

3.7. Particle size Distribution:

The layered pellets with 120% weight gain were tested for particle size distribution against the starter cores distribution using sieve analysis. In both cases, 100g of the pellets were placed on the top of the sieves set which contains the following sieve sizes, respectively ordered from the top to the bottom: 1mm, 0.8mm, 0.7mm, 0.6mm and 0.5mm sieve. Sieves set with the pellets was fixed on the shaker (Fritsch) and shaked for 10 minutes to distribute the pellets among the sieves. Distribution was calculated by weighing the pellets retained on each sieve.

3.8. Characterization of Drug-polymer mixtures:

3.8.1. DSC testing

The following samples were tested using DSC (TA instrument Q2000):

1. Diltiazem HCl raw material.
2. Kollicoat IR raw material.
3. Physical mixture of Diltiazem HCl and Kollicoat IR in 5:1 ratio.
4. Physical mixture of Diltiazem HCl and Kollicoat IR in 5:2 ratio.

Samples 3 & 4 were prepared by trituration of the two materials using mortar and pestle.

5. Co-evaporated mixture of Diltiazem HCl and Kollicoat IR in 5:1 ratio.
6. Co-evaporated mixture of Diltiazem HCl and Kollicoat IR in 5:2 ratio.

Samples 5 & 6 were prepared by dissolving drug and polymer in sufficient amount of water, then heating using hot plate at 85°C till evaporation of all water. The resultant solids were dried in static oven at 50°C for 5 hours.

5 to 10mg of the material was placed in aluminum crucible and hermetically sealed with its led. Test was done increasing the temperature by 10°C per minute up to 300°C which is higher than the drug and polymer melting points. Nitrogen gas flow was 50 ml/minute.

3.8.2. Water sorption and desorption of Drug-polymer mixtures:

This test was performed using DVS Advantage system by exposing the sample to different levels of humidity (at constant temperature of 25°C), this is to check the hygroscopicity of the material and at what humidity it will take a significant amount of moisture. Hygroscopicity is the ability of a substance to attract and hold water molecules from the surrounding environment through either absorption or adsorption, with the absorbing or adsorbing material becoming physically 'changed,' somewhat: by an increase in volume, stickiness, or

other physical characteristic of the material as water molecules become 'suspended' between the material's molecules in the process.

The European pharmacopeia is proposing a method for testing and defining the hygroscopic materials. This method is performed by placing a known weight of the material in a desiccator or a climatic cabinet set at 25°C and 80% relative humidity, allow to stand for 24 hours, then weigh the sample again. The result is interpreted as follows:

- Deliquescent: sufficient water is absorbed to form a liquid.
- Very hygroscopic: increase in mass is equal to or greater than 15%.
- Hygroscopic: increase in mass is less than 15% and greater than or equal 2%.
- Slightly hygroscopic: increase in mass is less than 2% and equal to or greater than 0.2%.

Knowledge of this physical property is important to predict the stability of the materials and dosage forms, and to determine the suitable packaging material in order to protect the product. If the materials are hygroscopic and not well protected by a proper package, the product will take significant amount of moisture during storage, and physical or chemical stability might be altered.

The chemical stability alteration could be drug degradation (if the drug is moisture sensitive) which will lead to drop in the drug assay or increase in the impurities levels more than allowed limits, which might be toxic, and then the product will not be approved.

The physical instability could be faced with moisture uptake as aging of the materials which can lead to hardening of the product or reduction in the dissolution rate of the product.

Tested samples were the following:

Diltiazem hydrochloride powder, Kollicoat IR powder and DTZ: KIR co-evaporated mixture in 5:2 ratio.

3.9. Layered pellets coating

The purpose of this stage is to apply the sustained release polymer as a film on the drug layered spheres by coating using Wurster column technique that has been used in the layering process.

The goal of this coating is to suppress the very fast release of the drug from the layered pellets to prolong its action and to achieve sustained release dosage form of pellets filled in capsules. Diltiazem HCl is a very water soluble drug, and this makes the control of its release a big challenge.

The polymer that was used for coating is Kollicoat SR 30D which is an aqueous dispersion of the water insoluble polyvinyl acetate.

Different levels of coating were applied to the pellets and the release profiles of the pellets were evaluated at each coating level. Also, the effect of plasticizer (5%) and curing of pellets on the drug release was evaluated.

All the coating work was done using pellets of trial 5 (120% drug-polymer loading). Kollicoat SR 30D was the coating polymer, and Triethyl citrate (TEC) was the plasticizer in 5% ratio of the dried polymer in all cases. The following are the trials have been performed:

Table 4: Coating loading levels

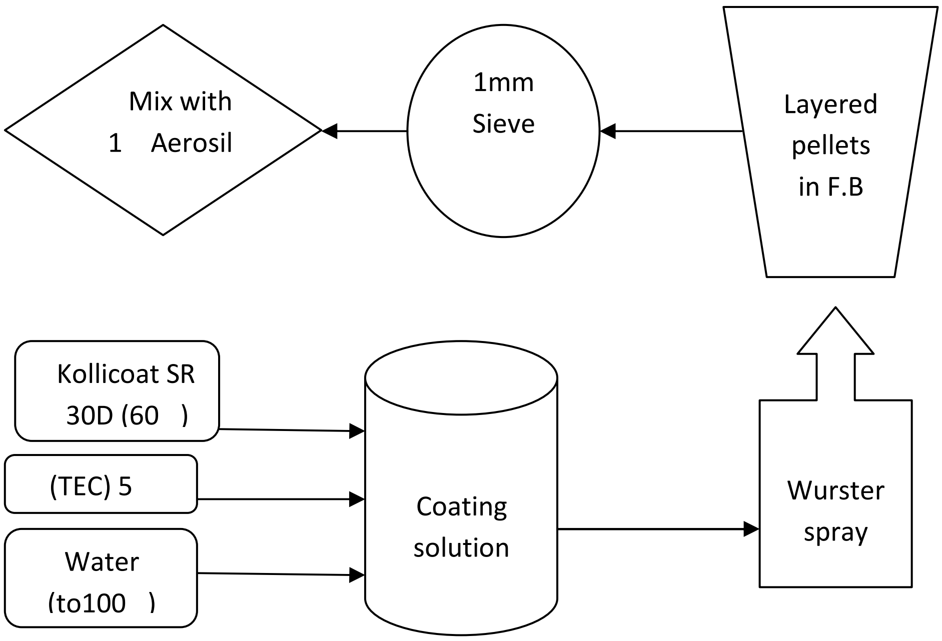
Coating Composition	Trial No.	Solids Loading weight (%)
Kollicoat SR 30D + 5% TEC	1	8
	3	15
	5	22
Kollicoat SR 30D	2	8
	4	15
	6	22

The coating solutions were prepared according to the following compositions, and spraying continued till the required weight gain was achieved.

Table 5: Coating solutions composition

composition	plasticized Trials (g)	unplasticized Trials (g)
Kollicoat SR	60	60
Triethyl citrate	0.8	0.0
Water q.s to	100 ml	100 ml

The manufacturing procedure is shown in the following flow diagram.



The manufacturing conditions in the fluid bed processor were monitored throughout the process and are presented in Table (6).

Table 6: Coating process parameters

Inlet air temperature	50-55°c
Outlet air temperature	35-38°c
Atomizing pressure	1.3 bar
Air flap	30
Pump speed	9rpm
Spraying rate	220 g/hr.

3.10. Curing of coated pellets

The effect of curing of the manufactured pellets on dissolution was evaluated. Part of each of the coating levels (about 50gm) was cured. Curing was done by placing the coated pellets exposed in a dish in static oven at 50°C for 24 hours. The resultant pellets were filled into colorless size zero capsules.

3.11. Appearance & Coating Weight gain

Pellets in all trials were tested visually for uniformity and freedom of agglomerates.

Actual weight gain was calculated by comparing the resulting actual weight after coating to the theoretical weight supposed to be achieved in each trial, multiplied with 100%.

3.12. Film flexibility testing:

To understand the dissolution behavior between plasticized and unplasticized coatings of the pellets, films for Kollicoat SR dispersion were prepared.

Two samples were prepared, one for Kollicoat SR dispersion as is, and the second for Kollicoat SR dispersion mixed with 5% (to the weight of the dried polymer) Triethyl citrate.

Both films were prepared by pouring the dispersion in a petri dish, leaving it at room temperature for three days, till liquid evaporation and getting a dry film.

3.13. Dissolution of coated pellets:

Dissolution studies were conducted in a USP dissolution apparatus II (Vankel) over a 24 hours period using 900 ml of deionized water as dissolution medium. The stirring rate and temperature were adjusted to 100 rpm and 37±0.5^{o}C, respectively.

At predetermined time intervals, 6 mL samples were withdrawn for analysis and immediately replaced with an equal volume of fresh medium maintained at the same temperature. The sample was diluted with water to 50ml in volumetric and a portion of the resultant solution was filtered using 0.45μm syringe filters before the absorbance of DTZ was measured at 237 nm (THERMO: Evolution 300 BB). DTZ concentration was calculated from linear calibration

plots. The dissolution tests were performed in triplicates and the mean values as well as standard deviations were calculated.

In all trials layered pellets were mixed with 1% Aerosil to prevent sticking and adhesion of the pellets during storage and upon dissolution testing, then filled into size zero colorless capsules according to its filling weight taking into consideration the assay results.

3.14. Effect of Aerosil on coated pellets

While performing the dissolution testing for the trials, when the capsule thrown in the dissolution vessel, the capsule shell dissolved within few minutes, but the pellets stayed as one mass in the vessel. This behavior was because of the tackiness of the surface of pellets once they exposed to water. This behavior could affect the dissolution results of the system, since the surface area of this aggregate mass is lower than the surface area of the separate pellets. However, this agglomeration is not acceptable and considered as a defect in the dosage form. As an instant solution the dissolution testing was performed by emptying the contents of the capsule (pellets) in the vessel, as a result, pellets were moving separately.

To solve the observed aggregation problem associated with the capsulated pellets, one percent of Aerosil 200 was mixed with the coated pellets, and filled in the hard gelatin capsules. Upon testing in the dissolution vessel and after dissolution of the shell, pellets found to be dispersed freely in the medium without any agglomeration. So, mixing with one percent Aerosil will be considered in all trials.

3.15. Thermal stability of coated pellets

The optimized multi-particulate beads were subjected to accelerated stability studies. The formulations were kept in close and open HDPE bottles, in a Stability chamber at 40 °C / 75 % relative humidity (RH) according to ICH conditions.

4. Results and Discussion

4.1. Appearance of layered and coated pellets:

Layered and Coated Pellets in all trials were tested visually and found to be spherical, uniform and free of agglomerates. In case of coated pellets they were glossy.



Figure 8: Picture of layered pellets

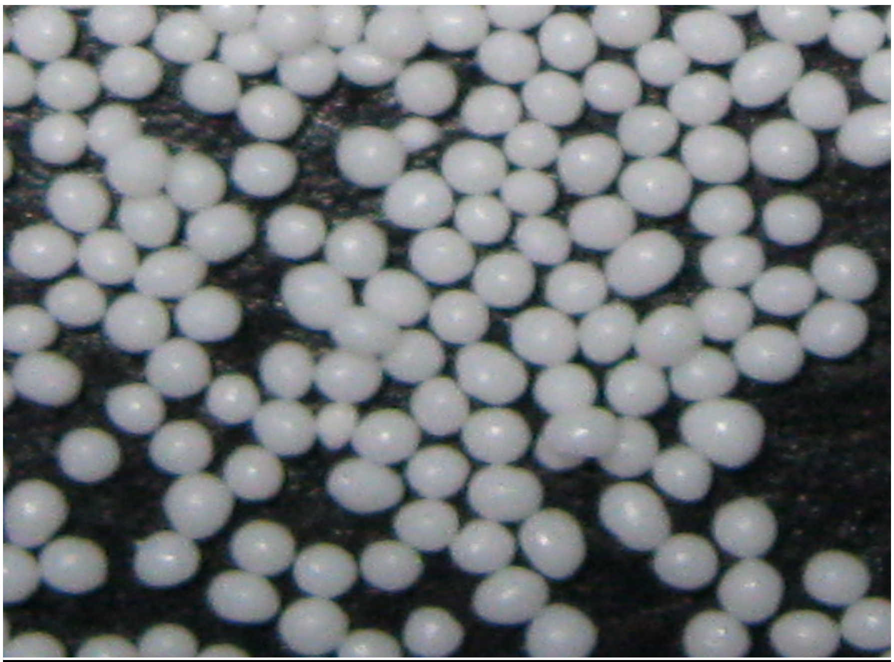


Figure 9: Picture of coated pellets

4.2. Analytical Method

Table 7: Concentration/ Absorbance for linearity.

Diltiazem HCl Concentration (%)	Absorbance at 237 nm
8	0.0725
16	0.1409
25	0.2116
50	0.4247
67	0.5566
100	0.824
133	1.1033

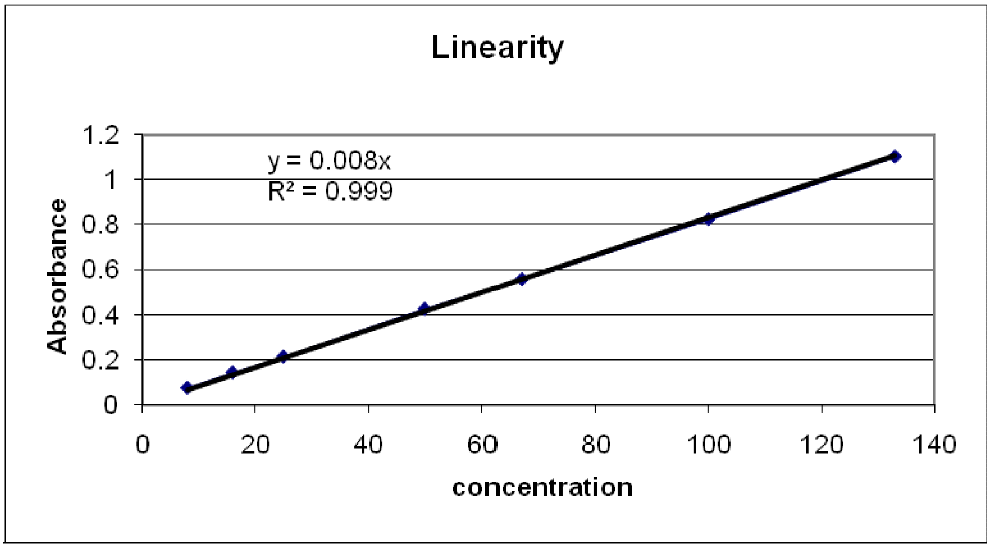


Figure 10: Linearity curve for Diltiazem assay.

The method was found to be linear in the range studied with, as can be seen in Figure (10).

4.3. Placebo Interference and selectivity:

The absorbance of the placebo at measurement wavelength was (0.01) which is equivalent to 1.3% of the active concentration. This interference will be considered acceptable and the method was considered selective.

4.4. Weight gain & Assay of layered & coated pellets:

4.4.1. Layered pellets

Table 8: Weight gain and Assay results of layering trials

Trial No.	Theoretical proposed weight (g)	Actual achieved weight (g)	Actual weight gain (%)	Assay (%)
1	680	646	95	97
2	668	646	97	94
3	812	795	98	96
4	808	760	94	95
5	1100	1020	93	92
6	880	845	96	98

Loading efficiency results showed an almost complete drug loading in all trials. Any loss is probably due to less than optimal process conditions and transfer losses rather than the effect of the formulation composition or the polymer and drug intrinsic properties.

It was concluded that increasing the (Drug-Polymer) ratio from (5:1) to (5:2) in order to improve binding properties and loading efficiency was not necessary and instead it caused an increased process time and the weight of pellets required to achieve the target dose without any advantage in terms of loading. This leads us to choose (5:1) ratio in future work.

The attempt to increase the drug loading up to 120% was achieved successfully allowing for the preparation of higher dose units using smaller finished dosage form weight and volume.

The results of Assay and weight gain were very close, which indicates good correlation between weight gain and loading efficiency and in case of trials where assay was slightly higher than actual weight gained, the reason might be attrition of the core pellets in the initial stage of the process, so the ratio of drug to the core pellets is higher than planned.

4.4.2. Coated pellets weight gain

In all trials the coating parameters were perfect enough to achieve 100% of the sprayed materials as weight gain.

4.5. Dissolution of active – layered pellets

Dissolution results for all trials were as following:

Table 9: Dissolution results of layered pellets

Time (min)	Average % Release					
	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6
15	97.8	94.8	100	101.9	104	96.5
30	95.4	100.7	98	100.8	104.6	98.7
45	97.6	100.9	98.7	99.9	104	98.2
60	99.4	106	98.3	100	103.8	98.6

The release of drug from the pellets in all trials is almost immediate and complete, since all drug released in the first 15 minutes, these results indicates that no effect of the polymer concentration in the solution on the release of the drug, and again lead us to consider the (5:1) ratio of drug-polymer solution. Runs with different loading weights showed similar release profiles.

This fast release is justifiable, considering the high solubility of DTZ in water, the solubility of the binding polymer and the presence of sink conditions

4.6. Particle size Distribution.

Table 10: Particle size distribution of starter spheres and 120% drug loaded pellets.

Mesh size	Size (mm)	Starter pellets (% retained)	120% loaded pellets (% retained)
18	1.0	Zero	Zero
22.5	0.8	Zero	18
25	0.7	Zero	50
30	0.6	2	28
35	0.5	96	4
Pan	Pan	2	Zero

It's clear as shown in the above table that the particle size of the pellets have been increased significantly after layering, as about 70% of the particles shifted from 500 µm to larger than 700µm. this new distribution represents the 120% weight gain level.

4.7. DSC of materials

4.7.1. Diltiazem HCl powder

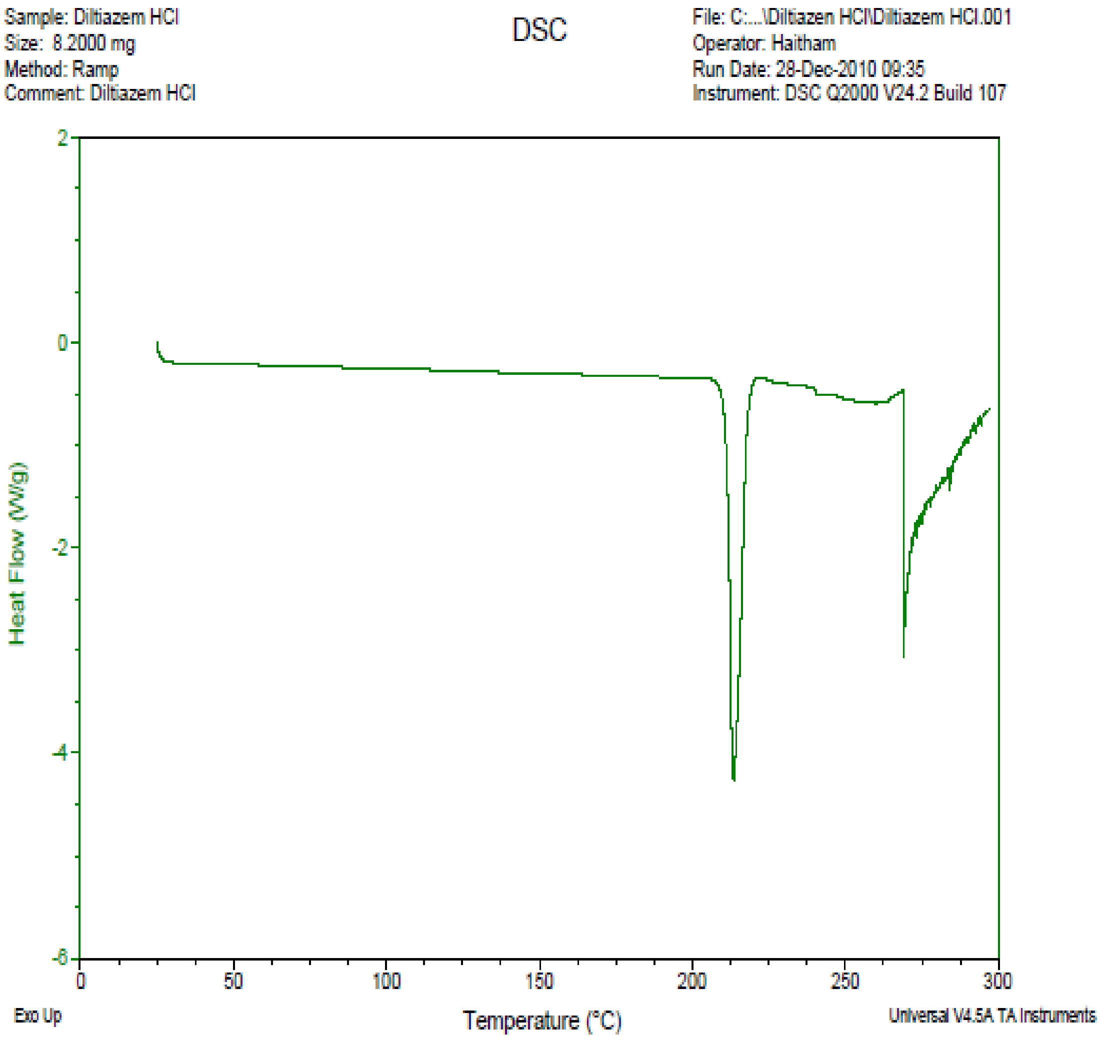


Figure 11: DSC of Diltiazem HCl powder.

This is the thermograph of Diltiazem HCl alone. The first peak at about 212°C is the melting point of Diltiazem HCl, which is matching with the stated value in the literature. The second peak at about 270°C is likely to be for degradation of the material.

4.7.2. Kollicoat IR powder

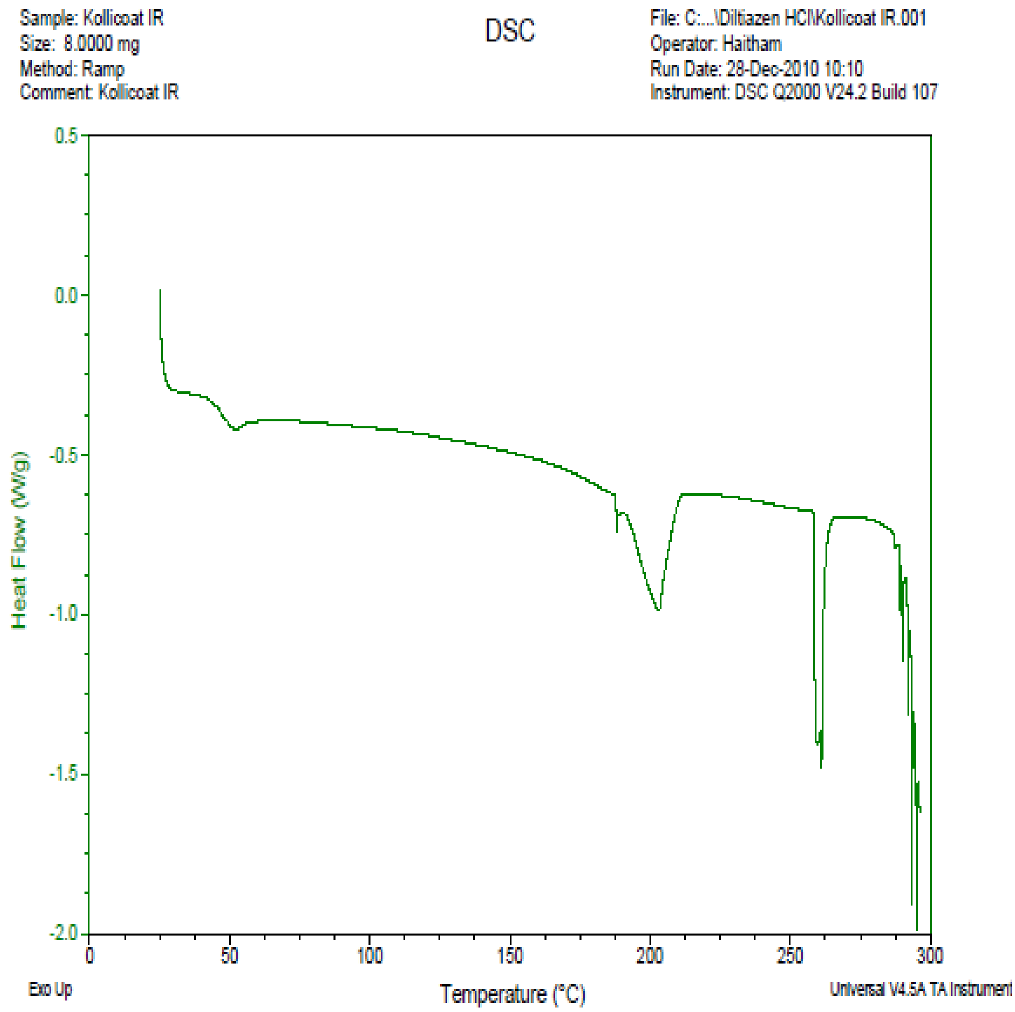


Figure 12: DSC of Kollicoat IR powder.

This is the Kollicoat IR thermograph, the first small peak at about 40°c is most likely to be glass transition of the polymer. The second peak at about 205°c is for the melting of the polymer. Third peak could be for material degradation.

4.7.3. Diltiazem - Kollicoat IR physical mixtures

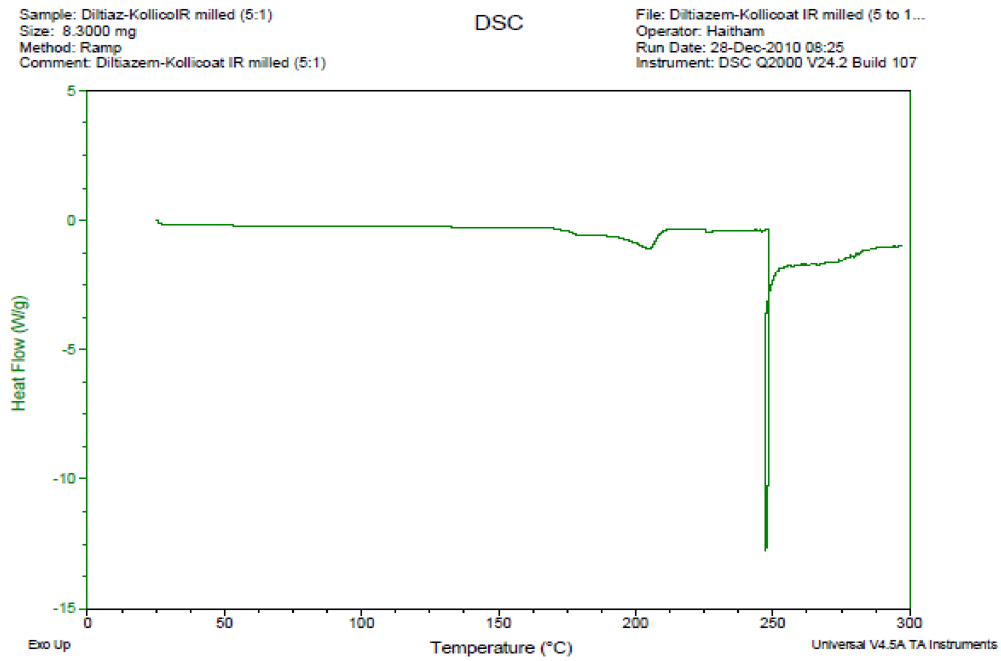


Figure 13: DSC of 5:1 Diltiazem - Kollicoat IR physical mixture.

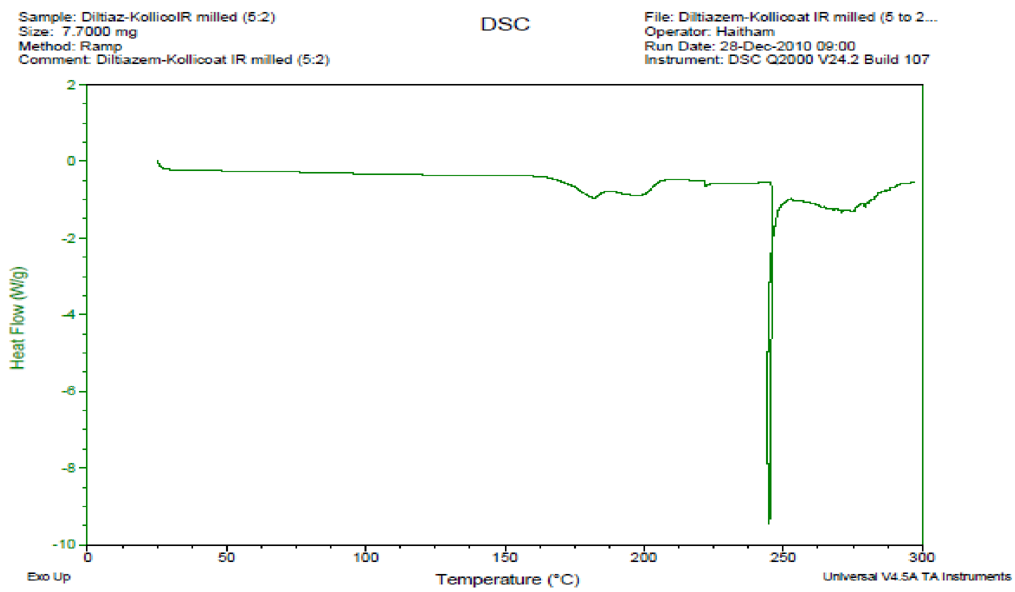


Figure 14: DSC of 5:2 Diltiazem - Kollicoat IR physical mixture.

4.7.4. Diltiazem - Kollicoat IR coevaporated mixtures

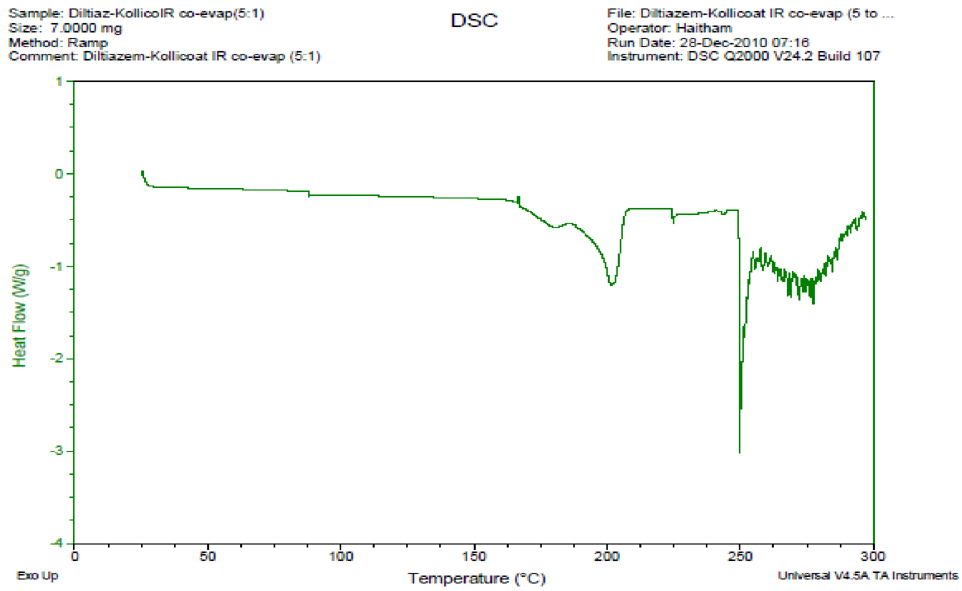


Figure 15: DSC of 5:1 Diltiazem - Kollicoat IR co-evaporated powder.

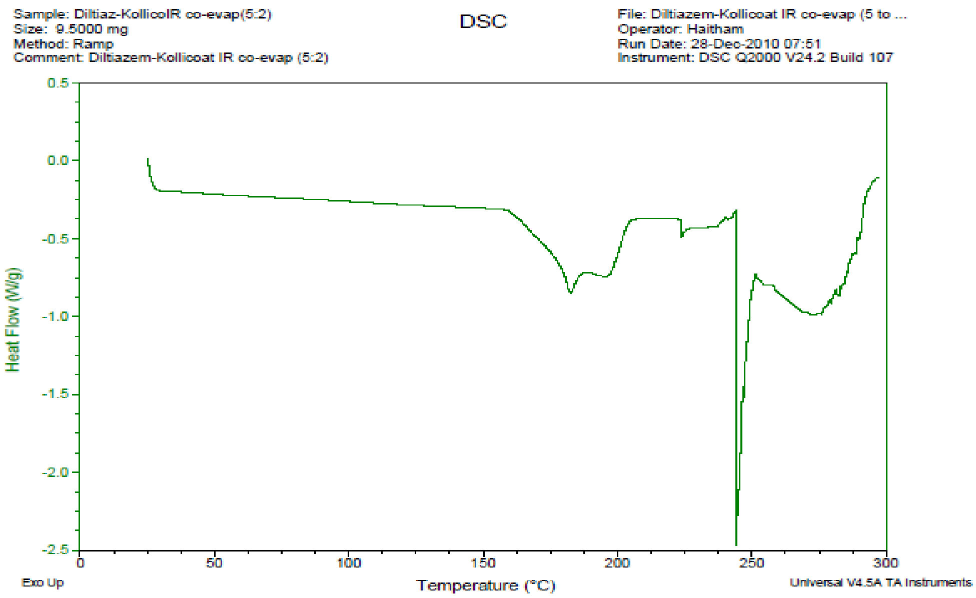


Figure 16: DSC of 5:2 Diltiazem - Kollicoat IR co-evaporated powder.

Discussion:

The main peak for melting for both materials was diminished in case of combinations; this behavior suggests physical interaction between the materials such as solid solution/dispersion formation.

4.8. Water sorption and desorption of Drug, polymer & mixture:

4.8.1. Diltiazem Hydrochloride powder:

Table 11: Sorption/ desorption data for Diltiazem HCl

Sample:		Diltiazem HCl - with Drying at 100 for 30min			
Temp:		24.9 °C			
Mass Ref:		17.0443mg from Mass at end of first 0.0 P/Po stage			
Target		**Change In Mass (%) - ref**			
Time (min)	**% P/Po**	**Sorption**	**Time (min)**	**Desorption**	**Hysteresis**
0	0.0	-0.0005	290	-0.0099	
24	10.0	0.0291	274	0.0174	-0.0117
34	20.0	0.0656	260	0.0508	-0.0148
45	30.0	0.1117	244	0.0950	-0.0167
60	40.0	0.1644	228	0.1542	-0.0102
75	50.0	0.2260	212	0.2188	-0.0072
91	60.0	0.3031	195	0.2985	-0.0046
107	70.0	0.3877	178	0.3837	-0.0040
124	80.0	0.5037	161	0.4939	-0.0099
141	90.0	0.6524	141	0.6524	

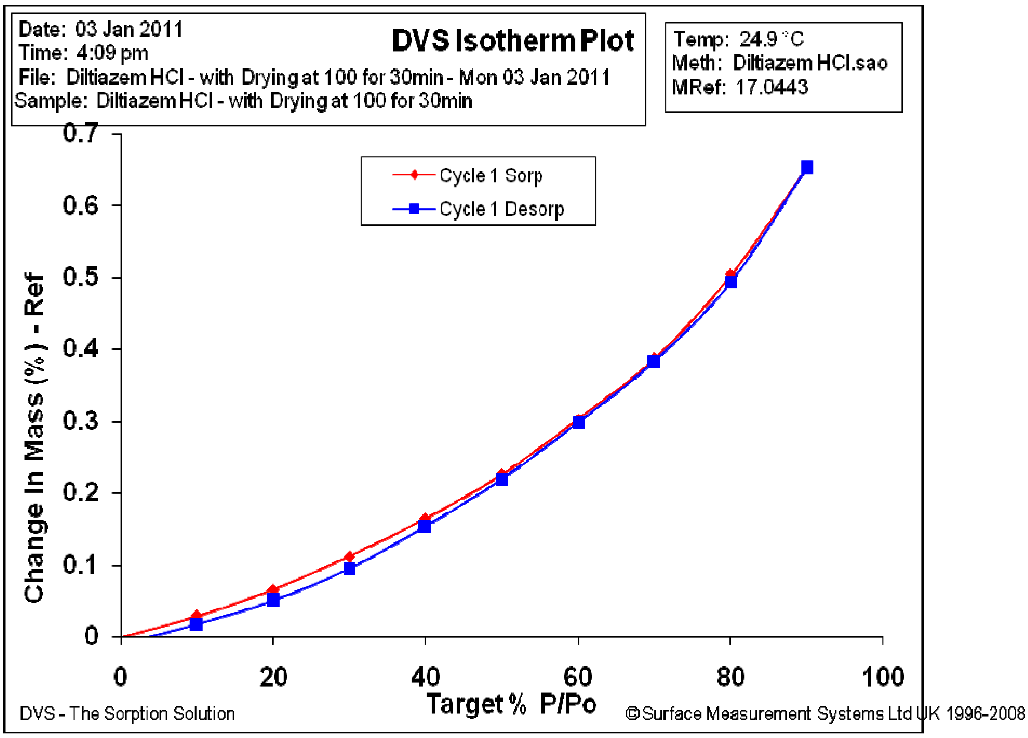


Figure 17: Sorption/ desorption curve for Diltiazem HCl

Discussion:

Sorption curve indicates that even at 90% humidity material has taken less than 0.6% moisture of its weight without any change in the appearance of the sample before and after testing. Desorption curve shows that with reduction in the humidity, material is losing its gained water, approximately at the same sorption rate. From the above data we can conclude that even Diltiazem hydrochloride is very water soluble material it is not hygroscopic, or according to the European pharmacopeia it is slightly hygroscopic.

4.8.2. Kollicoat IR powder:

Table 12: Sorption/ desorption data for Kollicoat IR

Sample:		Kollicoat IR- with Drying at 50 for 30min			
Temp:		25.1 °c			
Mass Ref:		10.6467 from Mass at end of first 0.0 P/Po stage			
	Target		**Change In Mass (%) - ref**		
Time (min)	**% P/Po**	**Sorption**	**Time (min)**	**Desorption**	**Hysteresis**
0	0.0	0.00	1494	0.07	
23	10.0	0.90	1462	1.18	0.28
50	20.0	1.77	1433	2.16	0.39
79	30.0	2.72	1397	3.34	0.62
109	40.0	4.24	1343	4.89	0.65
152	50.0	6.30	1285	7.14	0.84
201	60.0	9.50	1199	10.56	1.06
268	70.0	14.00	1078	15.17	1.17
361	80.0	22.59	837	23.59	1.00
524	90.0	39.85		39.85	

Discussion:

This polymer has shown hygroscopicity, the sorption curve indicates proportional increase in the adsorbed moisture with the increase of humidity in the environment. This moisture uptake reached about 40% of weight, but without any physical change on the powder. The loss of moisture in desorption phase was in the same rate and amount as moisture gained in the

sorption phase, and returned to the zero point. This is clear in the graph as there is almost no hysteresis between the two curves observed. So water is weakly bound to the material surface and can be lost easily without any change in the material. According to the European pharmacopeia this material is very hygroscopic.

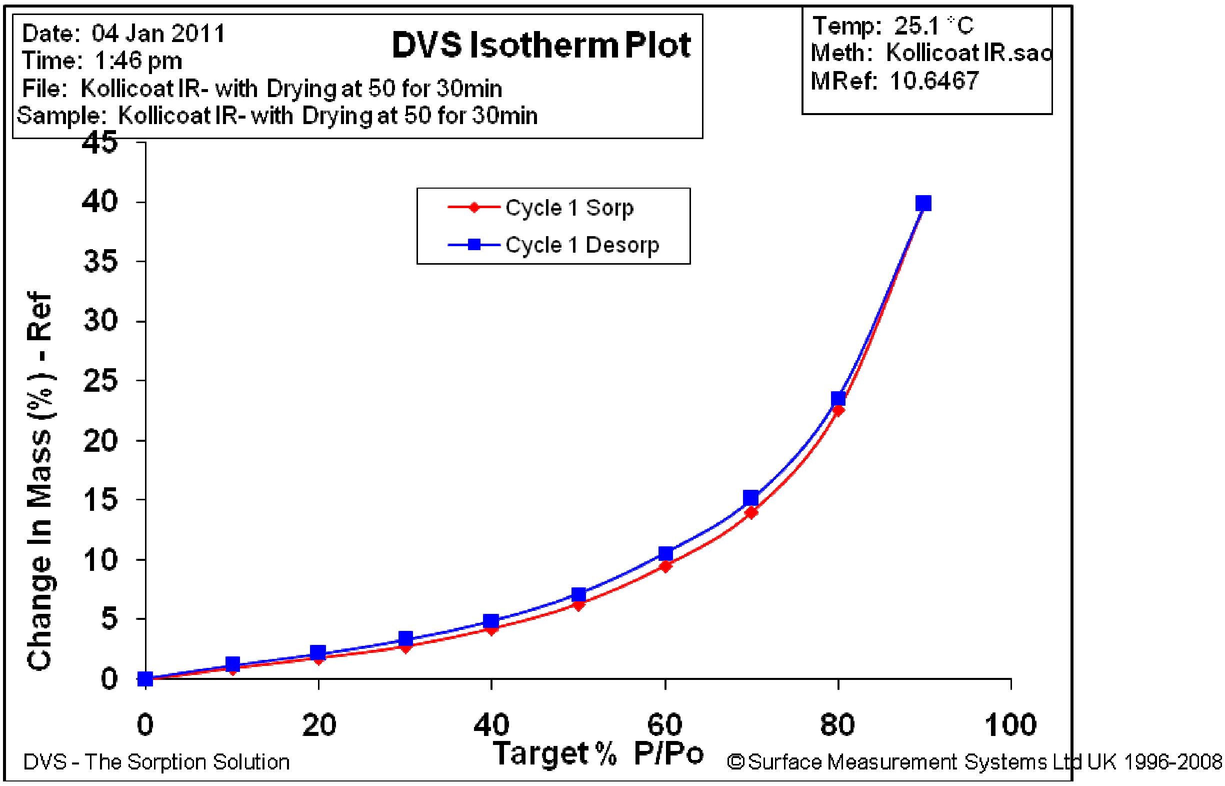


Figure 18: Sorption/ desorption curve for Kollicoat IR.

4.8.3. DTZ-KIR co-evaporated mixture:

Table 13: Sorption/ desorption data for DTZ- KIR co-evaporated mixture.

Sample:		Diltiazem -Kollicoat IR (5 to 2) co-evaporate			
Temp:		25.2 °C			
Mass Ref:		12.4356 from Mass at end of first 0.0 P/Po stage			
Target		**Change In Mass (%) - ref**			
Time (min)	**% P/Po**	**Sorption**	**Time (min)**	**Desorption**	**Hysteresis**
0	0.0	0.01	756	0.05	
24	10.0	0.27	735	0.35	0.08
46	20.0	0.57	713	0.67	0.09
67	30.0	0.93	688	1.07	0.14
89	40.0	1.39	653	1.58	0.19
114	50.0	1.99	613	2.25	0.26
142	60.0	2.97	576	3.35	0.39
180	70.0	4.23	509	4.66	0.43
223	80.0	6.64	417	7.27	0.63
285	90.0	11.79	285	11.79	

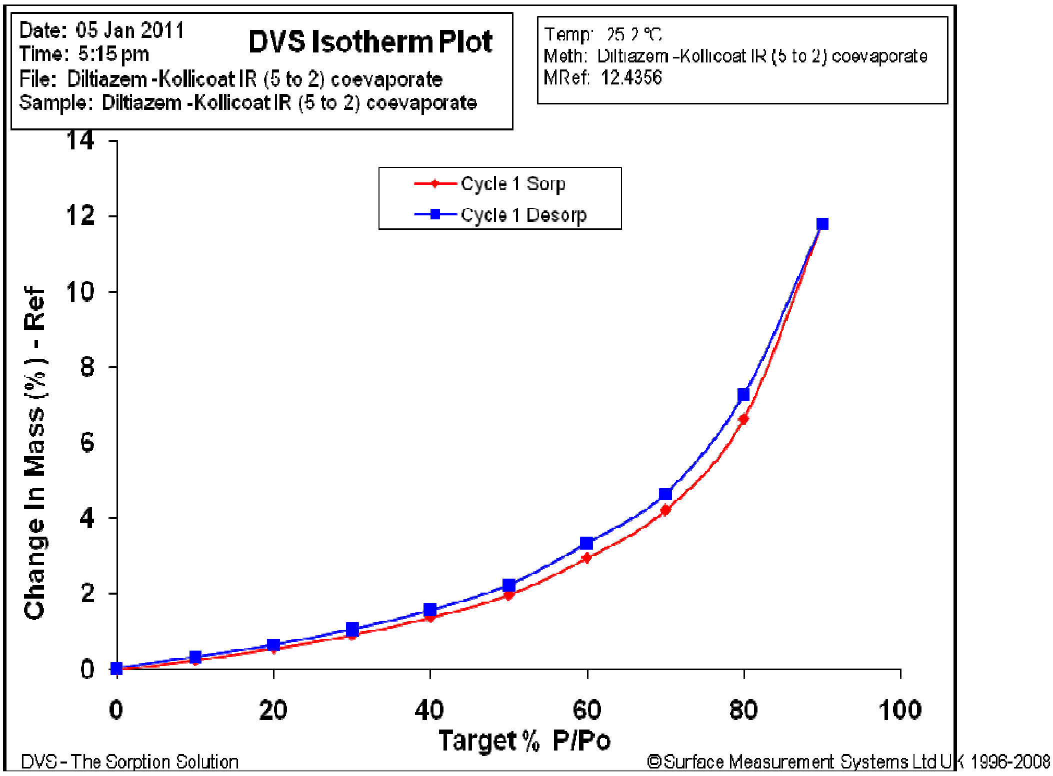


Figure 19: Sorption/ desorption data for Diltiazem HCl- Kollicoat IR co-evaporated mixture.

Discussion:

Mixture of the two compounds has lower affinity to moisture than the polymer and higher than the drug, the moisture uptake is equivalent to the polymer ratio in the mixture, so with the ratio we have used in our trials moisture uptake will be less (about 6%) as the ratio is 5:1. Of course more protection will be provided to the cores with the application of the water insoluble SR coating. Again the same behavior is observed in the desorption curve. According to the European pharmacopeia this mixture is slightly hygroscopic.

4.9. Film flexibility

Unplasticized film was rigid, glassy and fragile against any force applied to the film, while the plasticized film was very elastic and accepting folding to high extent.

4.10. Aerosil effect

Table 14: Dissolution results of pellets without plasticizer for Aerosil effect.

TIME (hour)	Average % Release					
	8% coating	8% coating Aerosil	15% coating	15% coating Aerosil	22% coating	22% coating Aerosil
0.5	65.4	36.6	6.2	3.6	2.1	2.2
1	83.9	59.1	11.2	4.7	2.7	2.3
2	95.2	84.5	36.6	22.8	10.8	7.0
4	100.4	96.4	57.8	53.6	32.4	25.3
6	101.3	99.3	80.2	70.8	51.3	35.2
8	101.7	100.7	87.9	81.4	64.3	46.0
10	103.5	103.0	92.4	86.8	74.9	55.9
12	103.1	102.1	96.0	91.4	78.2	65.2
16	104.5	104.2	99.8	96.9	90.4	80.1
20	105.4	102.8	103.5	98.8	99.9	91.1
24	105.0	101.5	104.2	99.0	103.0	95.6

Table 15: Dissolution results of pellets with plasticizer for Aerosil effect.

TIME (hour)	Average % Release					
	8%+TEC	8%+TEC Aerosil	15%+TEC	15%+TEC Aerosil	22%+ TEC	22%+ TEC Aerosil
0.5	**14.8**	**15.0**	**13.0**	**8.0**	**4.5**	**2.7**
1	**26.1**	**25.7**	**11.3**	**8.6**	**5.3**	**3.3**
2	**58.8**	**59.1**	**18.2**	**16.3**	**7.7**	**4.7**
4	**84.0**	**84.5**	**32.3**	**35.2**	**11.4**	**7.6**
6	**90.3**	**92.9**	**43.9**	**51.6**	**14.5**	**12.0**
8	**94.7**	**98.2**	**55.5**	**63.5**	**20.4**	**17.9**
10	**98.9**	**100.4**	**65.5**	**72.6**	**26.1**	**23.9**
12	**101.1**	**101.6**	**72.0**	**78.5**	**33.2**	**33.0**
16	**101.7**	**103.2**	**86.3**	**88.6**	**49.0**	**48.4**
20	**102.7**	**103.2**	**94.8**	**95.0**	**63.4**	**68.9**
24	**103.0**	**102.0**	**101.9**	**99.7**	**78.1**	**80.5**

The dissolution profiles for the plasticized coatings have not been changed with the addition of Aerosil. In the other hand, unplasticized coatings release rates have been reduced with the addition of Aerosil. The reason might be related to the hydrophilicity of the Aerosil and its ability to take water; this can help to mature the coalescence of the film and improves its function. Since Aerosil has a consistent effect on all coating levels it was used in all other dissolution tests as a lubricant to prevent pellets coagulation in dissolution vessel.

4.11. Curing effect on coated pellets

After exposing the coated pellets to 50°C for 24 hours, the dissolution was tested against the unexposed pellets, and results were shown in the following figures (20 to 25).

The appearance of the pellets was the same before and after curing.

The release profiles of the cured and uncured pellets at 8% coating level were demonstrated in below figures. (Time (hrs) VS Release %).

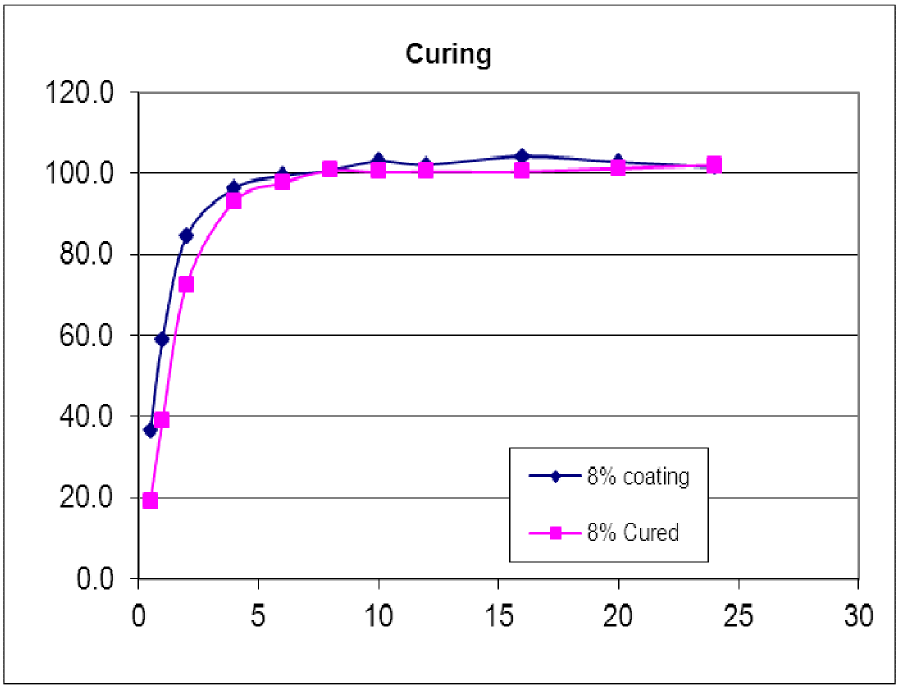


Figure 20: effect of curing on the release profile of 8% unplasticized coated pellets

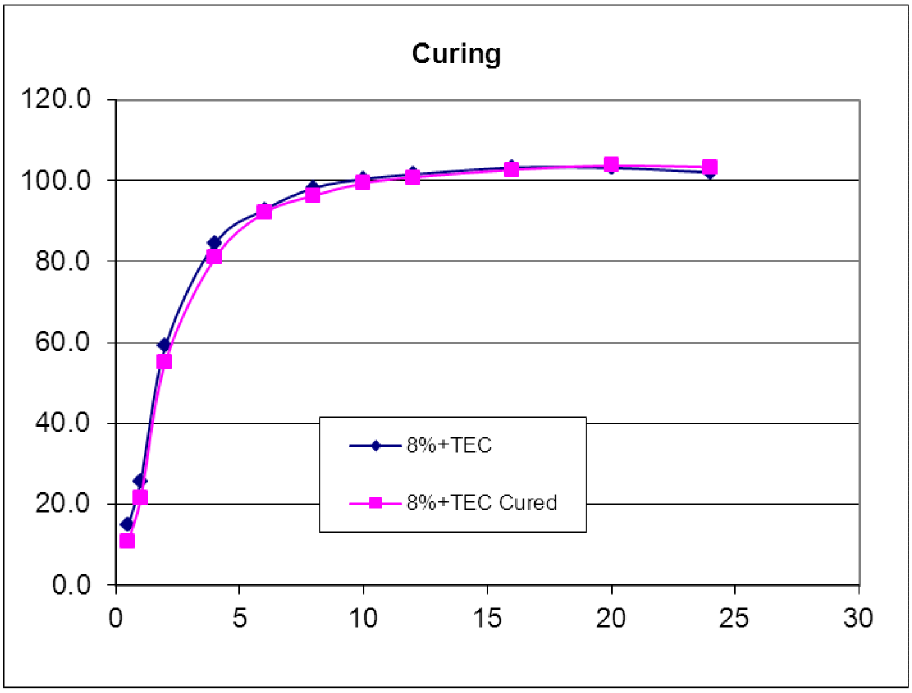


Figure 21: effect of curing on the release profile of 8% plasticized coated pellets

The release profiles of the cured and uncured pellets at 15% coating level were demonstrated in the below figures. (Time (hrs) VS Release %).

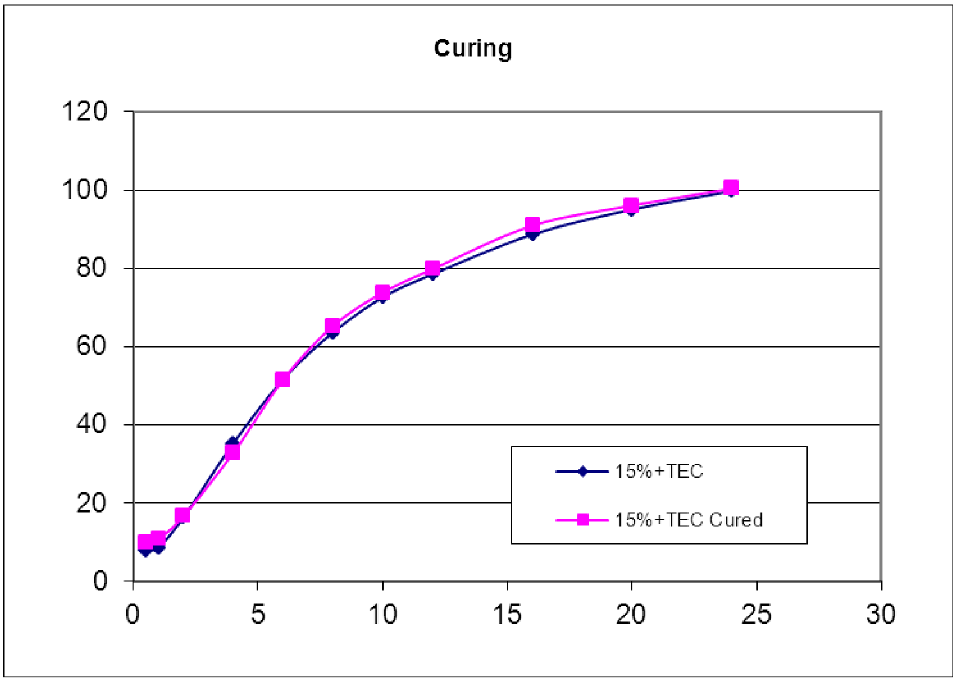


Figure 22: effect of curing on the release profile of 15% plasticized coated pellets

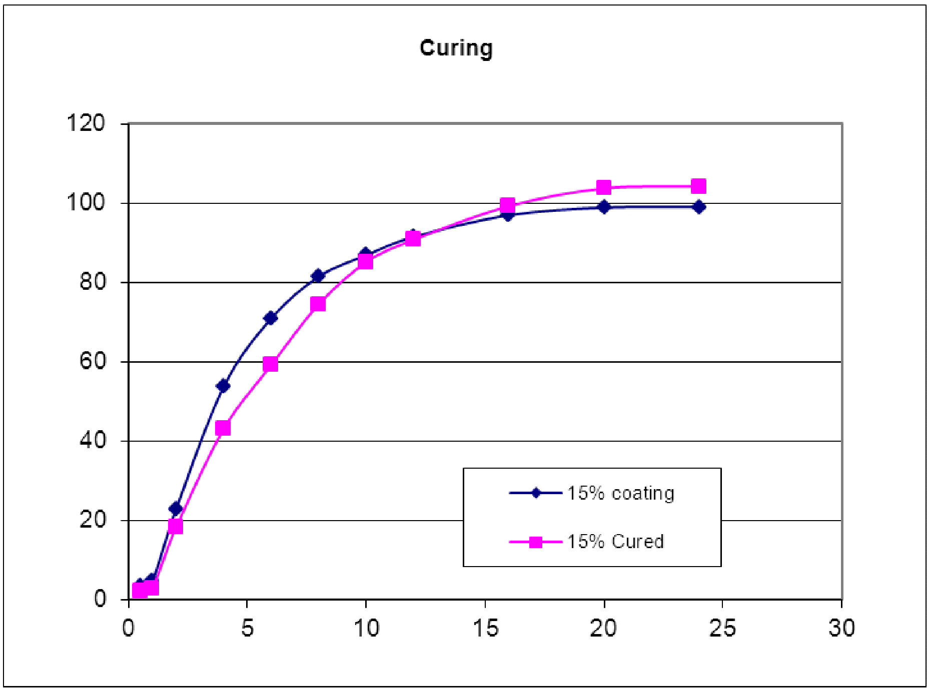


Figure 23: effect of curing on the release profile of 15% unplasticized coated pellets

The release profiles of the cured and uncured pellets at 22% coating level were demonstrated in the below figures. (Time (hrs) VS Release %).

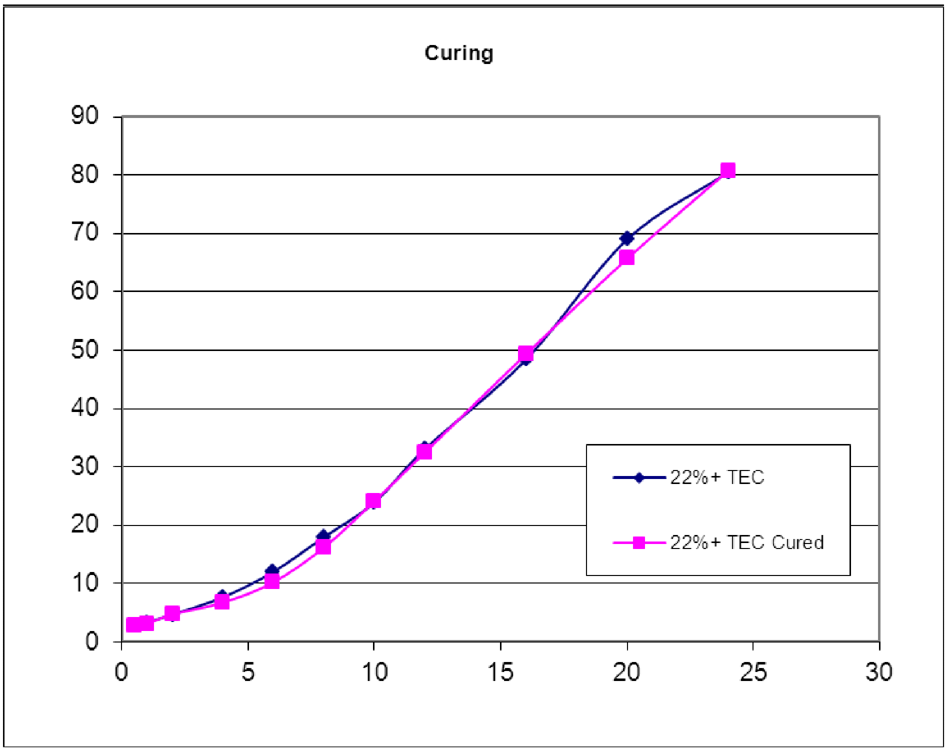


Figure 24: effect of curing on the release profile of 22% plasticized coated pellets

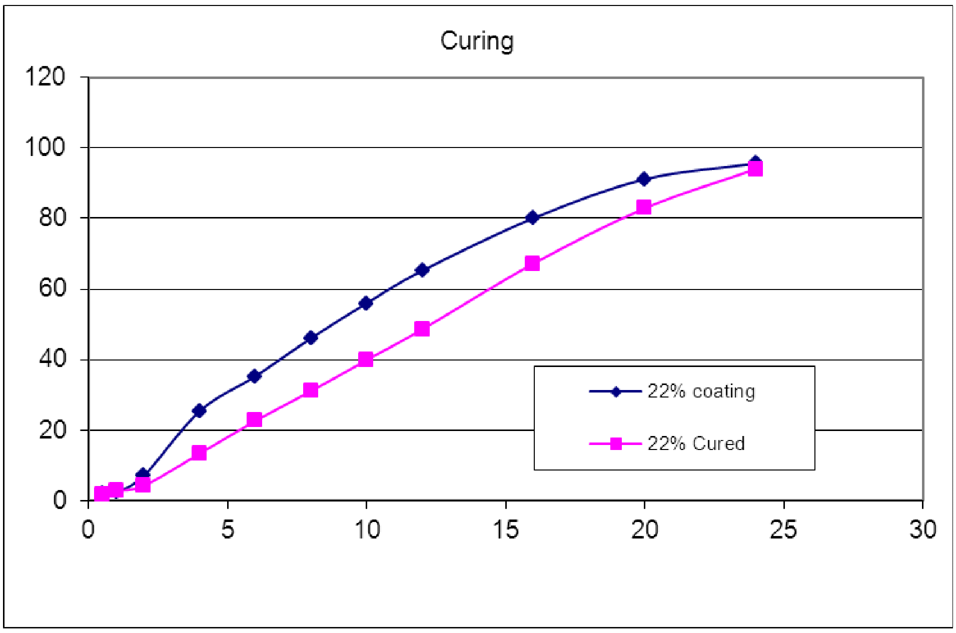


Figure 25: effect of curing on the release profile of 22% unplasticized coated pellets

What curing can do is to complete coalescence of the polymer spheres, depending on the coating formulation and conditions employed during coating. The mechanism of film formation from aqueous pseudo-lattices of water-insoluble polymers, such as Kollicoat SR 30D, is very different from simple deposition of a polymer from solvent-based coatings. Water evaporation concentrates the polymer particles in a closely packed arrangement on the substrate surface, and the capillary force of the interstitial water deforms the particles to cause coalescence and produce a dense, continuous film. When the coated substrates are cured at a temperature higher than the Minimum Film Forming Temperature, the interstitial water in the coating layer will ensure an adequate capillary force for the completion of film coalescence (Alkhatib, H. et al. 2005). Over drying remains a leading cause of partial coalescence and associated problems, particularly decreasing release rates on storage due to further gradual coalescence.

By comparing between the cured and uncured products using the above data we can conclude the following:

In the case of plasticized coatings in all trials, the release profiles have not been changed significantly by curing process, which means that plasticized films were completely coalesced during the manufacturing process, and the curing process added no value to the film.

In the case of unplasticized coatings, curing has reduced the release rate from the products of all coating levels if compared with the uncured product of the same coating level. This led us to conclude that the unplasticized films were not properly coalesced during the coating process, and curing led to the coalescence completion.

If we compare the release profiles of the cured coatings of the unplasticized films with the release profiles of the plasticized films at the same coating level, we can see that the release rate from cured unplasticized is faster, indicating the presence of cracks which will act as channels for the release of drug besides the normal diffusion through the intact membrane.

4.12. Dissolution of coated pellets

4.12.1 Effect of coating level

Dissolution profiles were generated for the three levels of coating with and without plasticizer, the results are collected in the following figures. (Time (hrs) VS Release %).

4.12.1.1. Unplasticized films

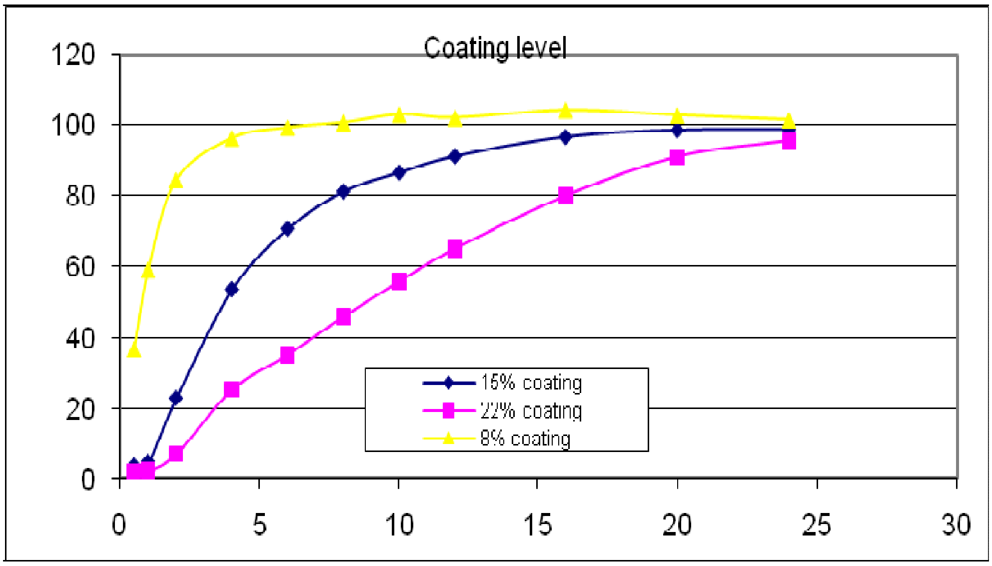


Figure 26: dissolution profiles for unplasticized pellets with different levels of coating

4.12.1.2. Plasticized films

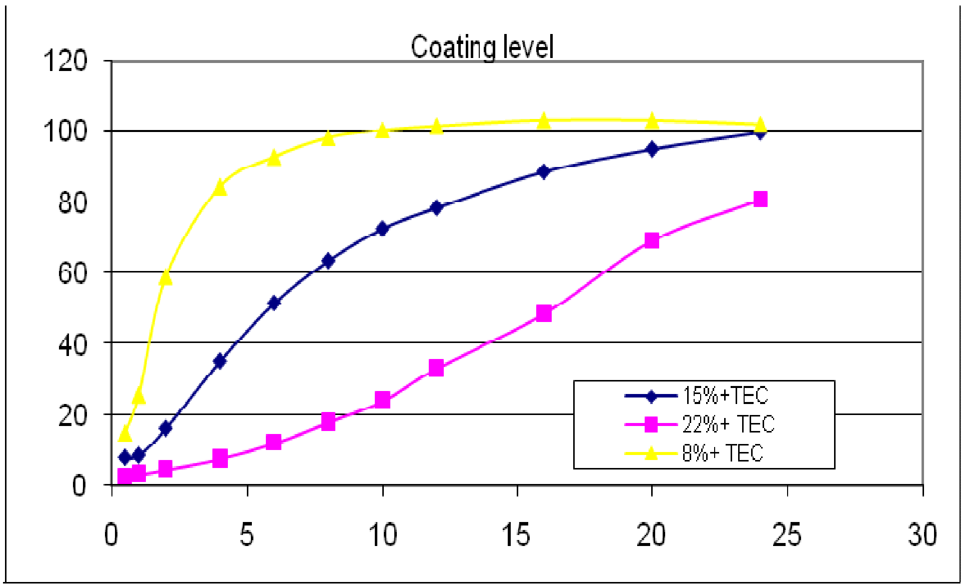


Figure 27: Dissolution profiles for plasticized pellets with different levels of coating

It is obvious from the above tables and graphs that the rate of drug release from the pellets is inversely proportional to the level of coating applied to the pellets; i.e. increasing the level of coating reducing the rate of drug release from the pellets. This is logic as with increasing the level of coating, higher thickness of the membrane will be applied, and the diffusion distance will be more.

In case of perfect reservoir system when the film is the rate-limiting barrier, the release kinetics will be zero-order (as long as a concentration gradient is maintained in the bead).

As we can see in the three coating levels above, with more coating thickness the release rate behaves close to zero-order kinetics for longer time, suggesting that constant drug diffusion through the film is maintained for longer time.

In case of 8% loading the release is prolonged for about 5 hours only, indicating that the coating amount applied is not sufficient to get the required release profile which is about 24 hours coverage.

In the second level of 15% loading, the release rate profile is acceptable in case of plasticized film, as release is gradual and complete through over the 24 hours. In the unplasticized film the release is faster and complete in 12 hours, the reason will be discussed in the next part.

With 22% loading, the release of the unplasticized film is perfect and exactly what we need regarding rate and extent. With plasticized film the release is extensively retarded, and this is not required.

4.12.2. Effect of plasticizer

The release profiles of the plasticized and unplasticized pellets for all coating levels were demonstrated in the below figures. (Time (hrs) VS Release %).

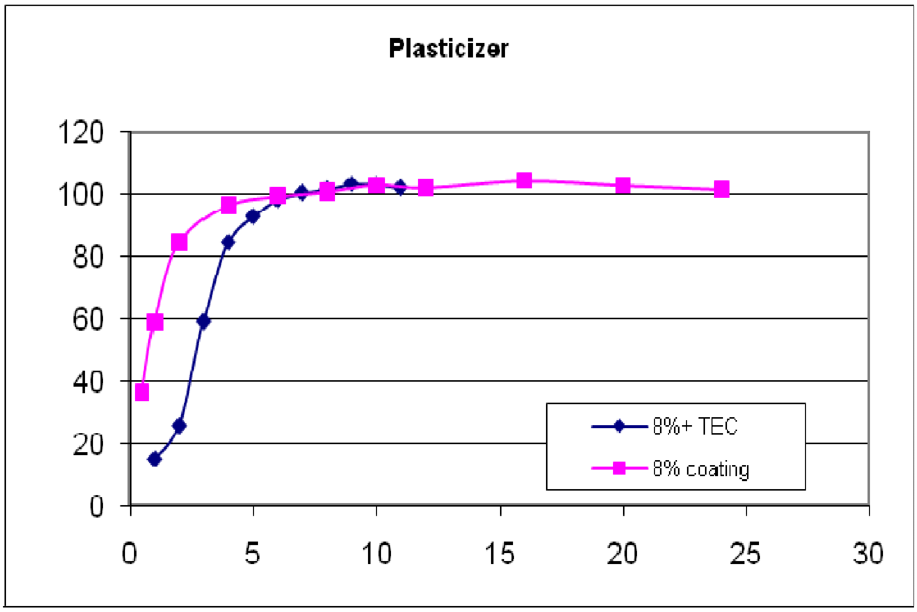


Figure 28: effect of plasticizer on the release profile of 8% coated pellets

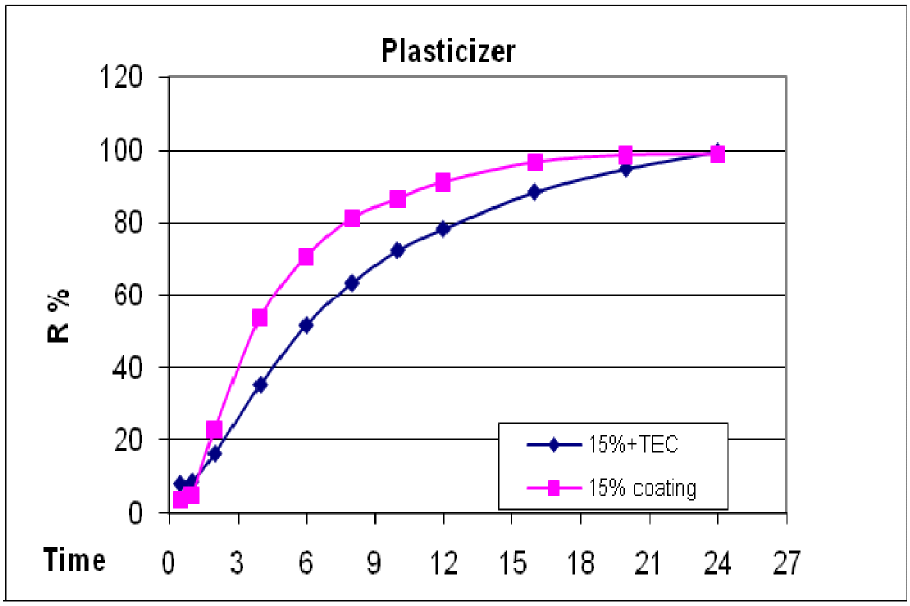


Figure 29: effect of plasticizer on the release profile of 15% coated pellets

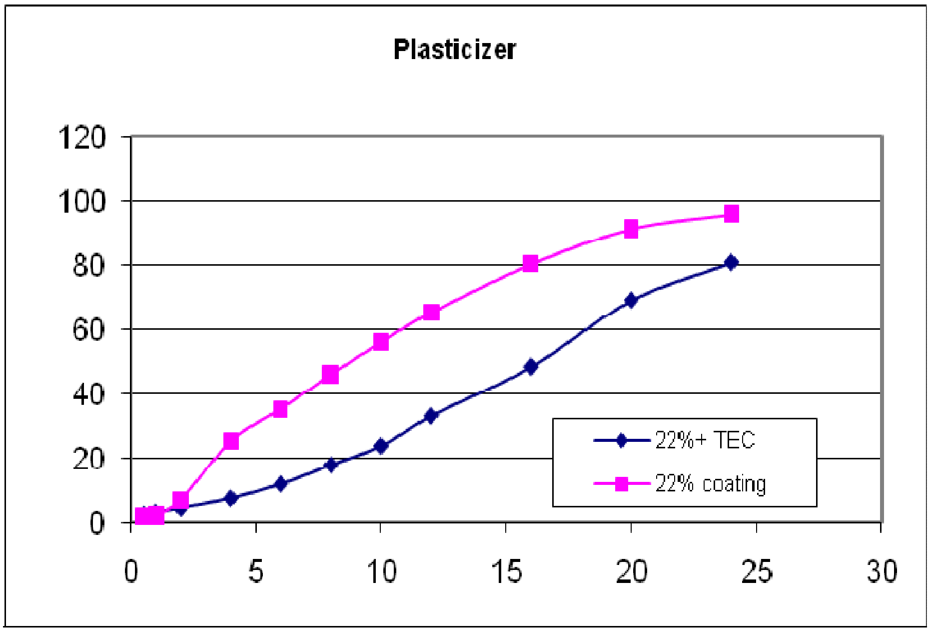


Figure 30: effect of plasticizer on the release profile of 22% coated pellets

The effect of plasticizer is clear in all coating levels, as we can see in the above data; the release rate from the plasticized films is slower than the release rate from the unplasticized films. This is can be explained by looking to the observations in the characterization of Kollicoat SR films above.

In case of plasticized coating, the film surrounding the pellet will be perfectly coalesced, elastic and free of ruptures or cracks which could be caused by attrition during the long coating process. So, the only way for the drug to leave the system is to diffuse through the intact film.

In the other hand, for unplasticized coating, the film surrounding the pellet will be rigid and fragile, and could be suffering easily from ruptures and cracks during the process. So the drug can leave the system by the usual diffusion through the membrane besides leaving through the small cracks.

As a result, the amount released from unplasticized coatings was more than it in plasticized coatings in relation to time.

4.13. Thermal stability of coated pellets

After incubation of the coated pellets for 1, 2 and 3 months in closed and open HDPE bottles at accelerated conditions (40°c & 75% RH), the dissolution behavior of the pellets was evaluated and presented in the following figures. (Time (hrs) VS Release %).

4.13.1. Level of 8% (unplasticized)

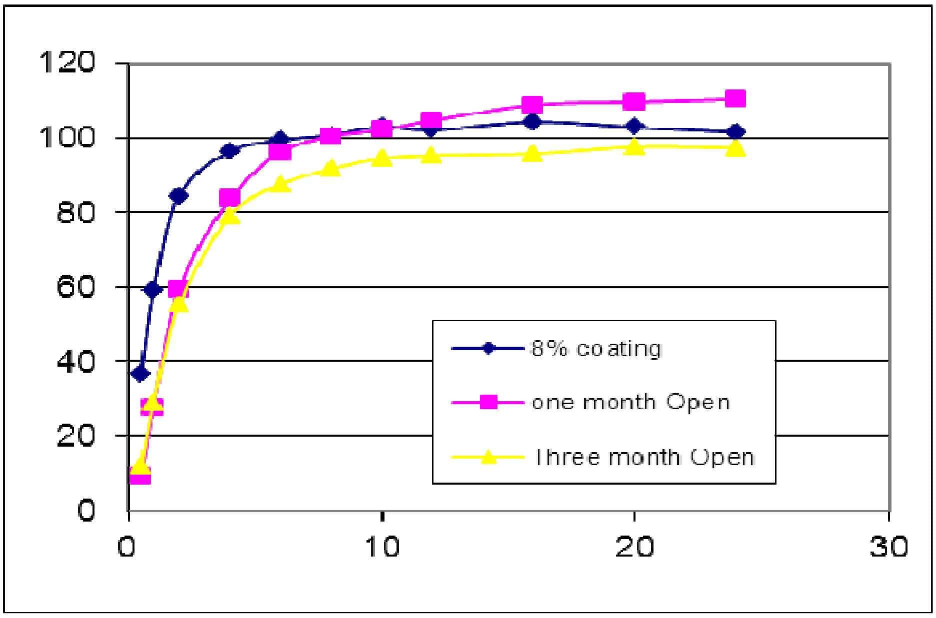


Figure 31: thermal stability dissolution results of 8% unplasticized coating (open)

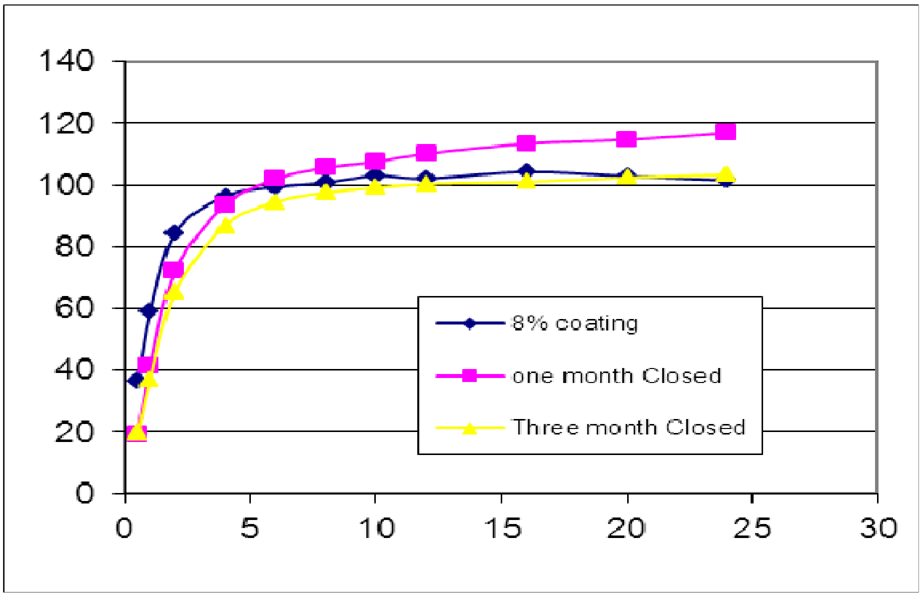


Figure 32: thermal stability dissolution results of 8% unplasticized coating (closed)

4.13.2. Level of 8% (plasticized)

Opened bottles

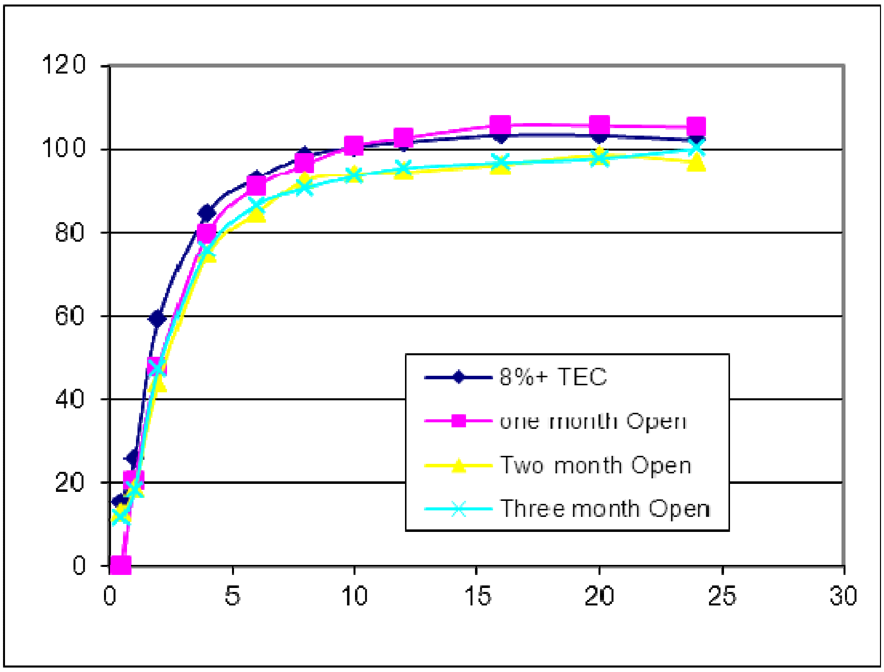


Figure 33: thermal stability dissolution results of 8% plasticized coating (open)

Closed bottles

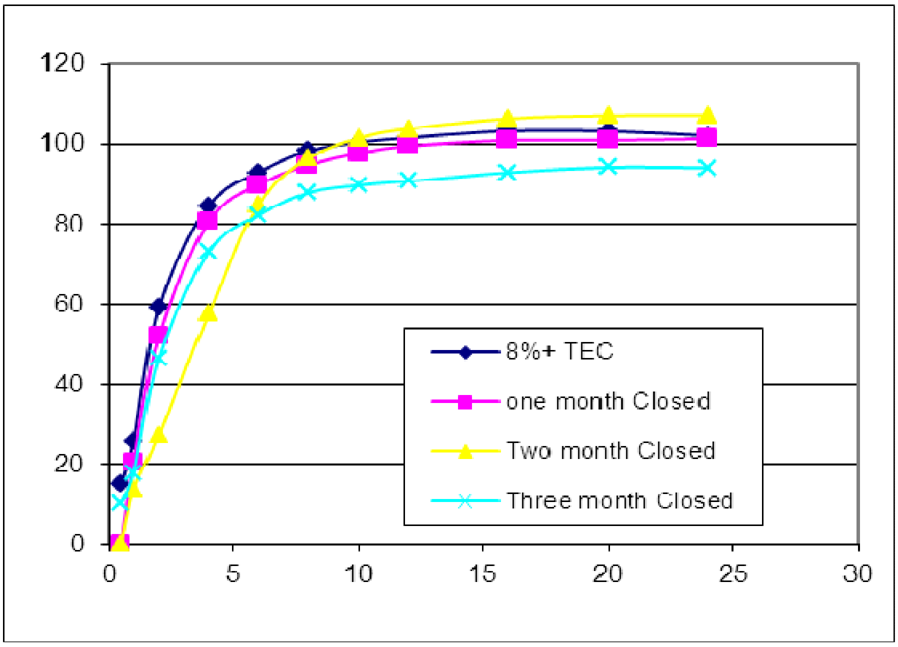


Figure 34: thermal stability dissolution results of 8% plasticized coating (closed)

4.13.3. Level of 15% (unplasticized)

Opened bottle

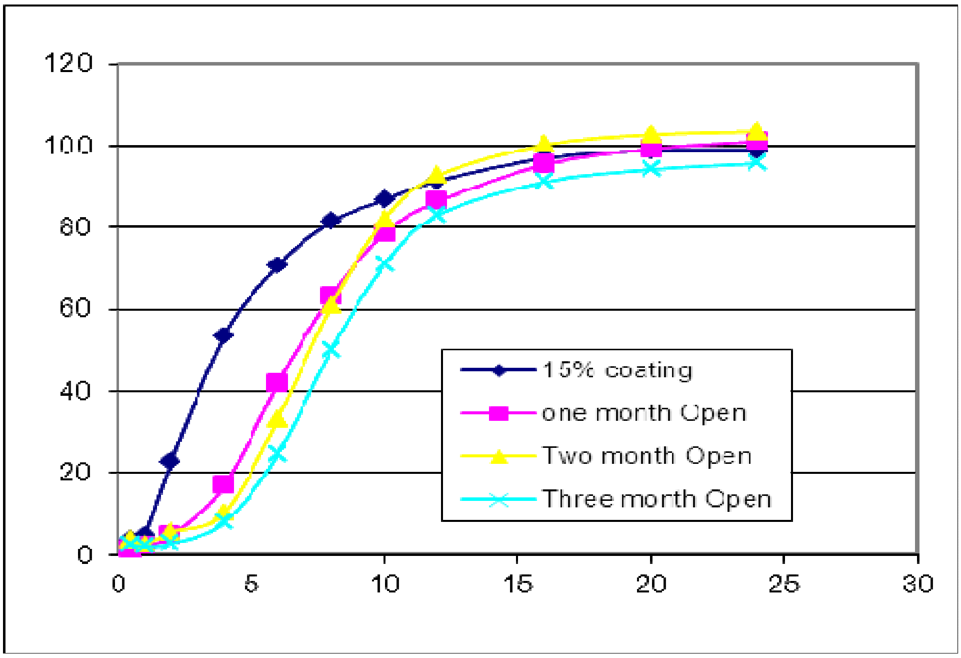


Figure 35: thermal stability dissolution results of 15% unplasticized coating (open)

Closed bottles

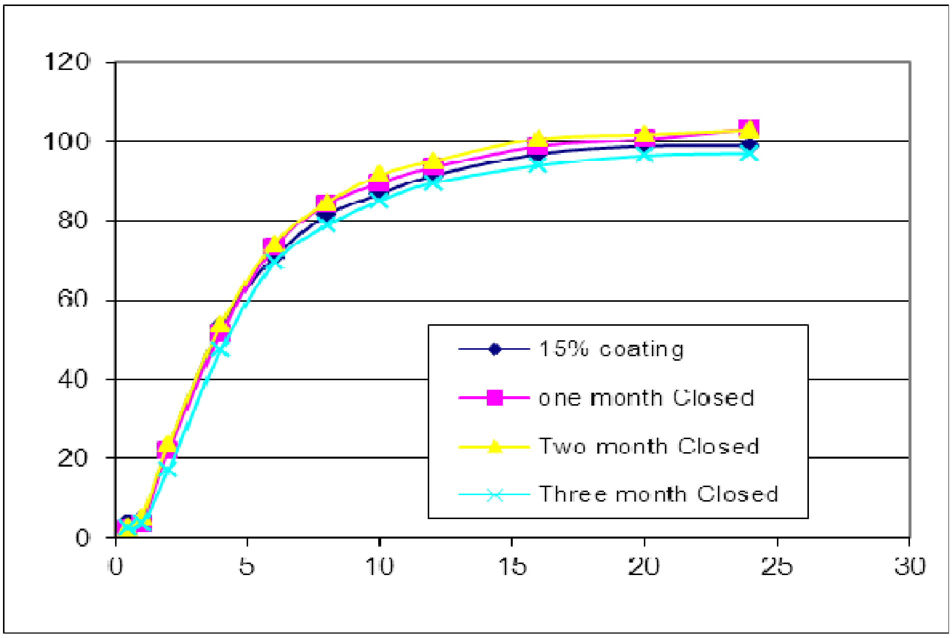


Figure 36: thermal stability dissolution results of 15% unplasticized coating (closed)

4.13.4. Level of 15% (plasticized)

Opened bottles

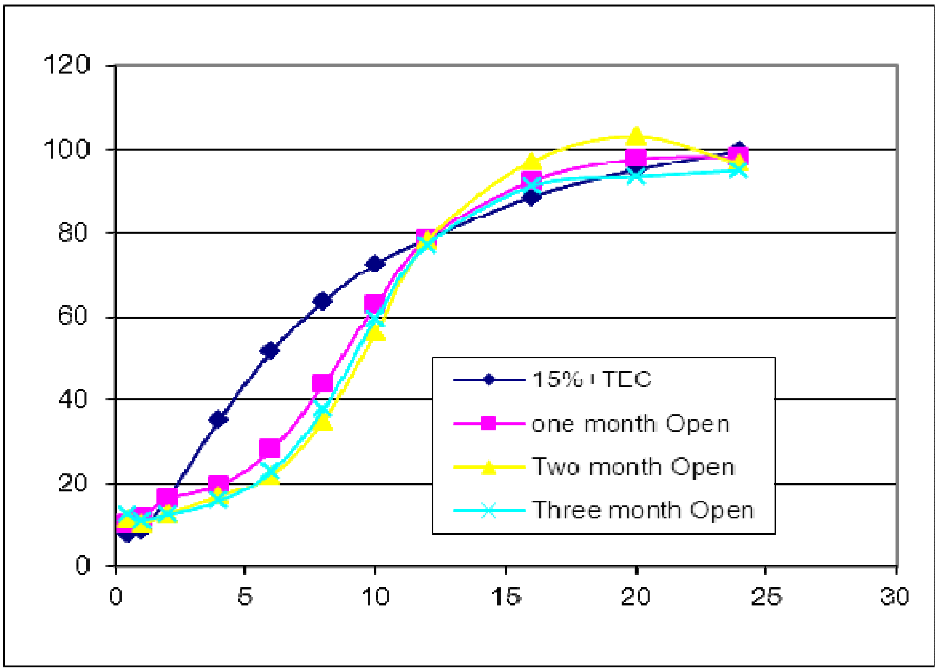


Figure 37: thermal stability dissolution results of 15% plasticized coating (open)

Closed bottles

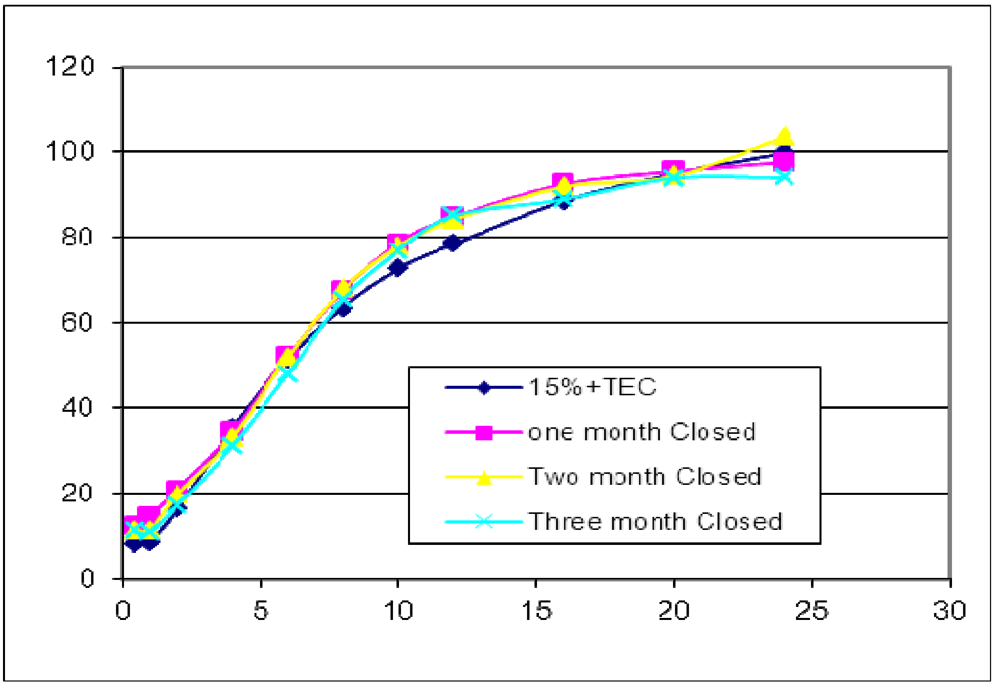


Figure 38: thermal stability dissolution results of 15% plasticized coating (closed)

4.13.5. Level of 22% (unplasticized)

Opened bottles

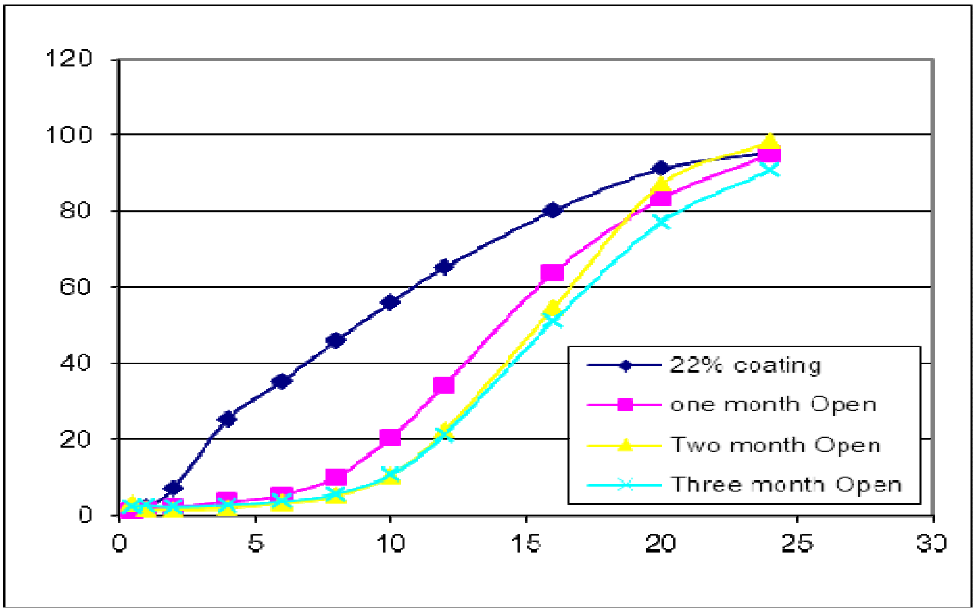


Figure 39: thermal stability results of 22% unplasticized coating (open)

Closed bottles

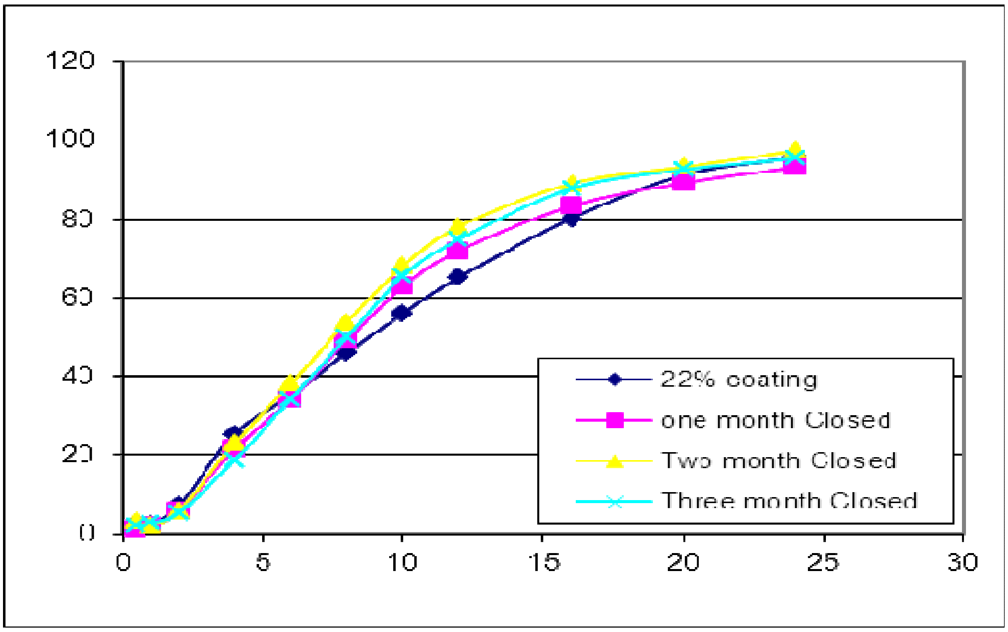


Figure 40: thermal stability results of 22% unplasticized coating (closed)

4.13.6. Level of 22% (plasticized)

Opened bottles

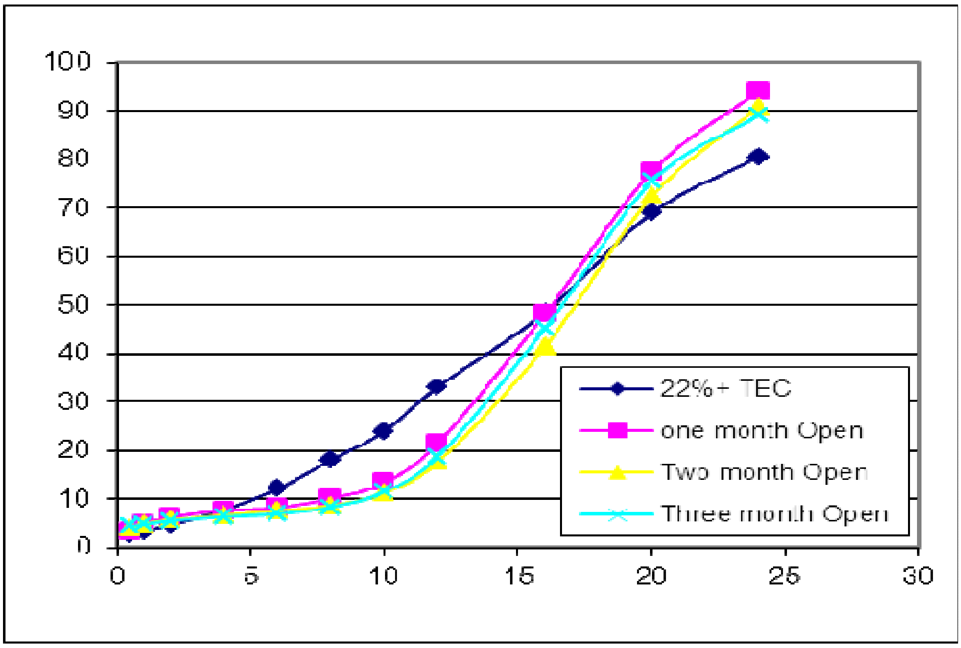


Figure 41: thermal stability results of 22% plasticized coating (open)

Closed bottles

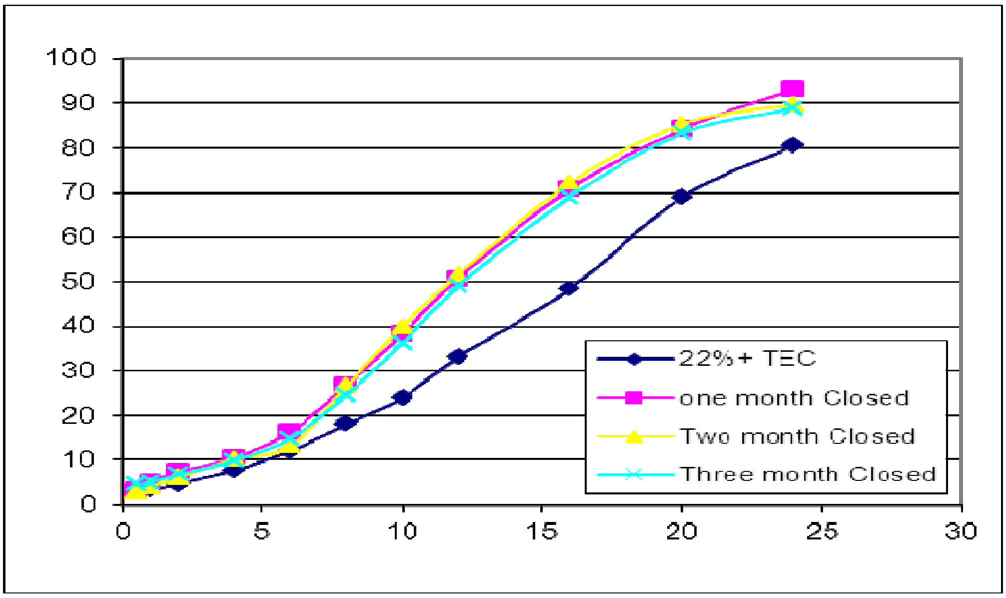


Figure 42: thermal stability results of 22% plasticized coating (closed)

The above thermal study is evaluating polymeric coating response to the effect of elevated temperature and humidity as in case of open bottles, and elevated temperature only as in case of closed bottles (which will provide protection from moisture) with time.

Significant decreases in release rate were observed in case of open bottles in which the pellets are exposed to moisture; elevated relative humidity results in further polymer particle coalescence during storage and, thus, denser film structures with lower water and drug permeability. This decrease in open bottles was more significant in unplasticized films which are less mature, even plasticized films showed some decrease in release rate (Alkhatib, H. et al. 2010).

Pellets in closed bottles were less affected even unplasticized films. This is because no moisture is present, as moisture is acting as plasticizer and has the major role in the coalescence process. So good packaging of this product has an important role in preserving the quality of the product during storage within the shelf life (Alkhatib, H. et al. 2005).

5. Conclusion

The objective of the study was achieved by successfully formulating the high dose, highly water soluble model drug into a controlled – release, multiparticulate dosage form using active layering technique in a Wurster – column, bottom-spray, fluid bed processor, with high loading efficiency reaching 120% of the initial cores weight, and robust, reproducible manufacturing parameters. Our model drug was Diltiazem Hydrochloride.

Binder level (Kollicoat IR) in the layering solution was chosen to be 20% of the drug substance rather than 40%, as the layering process was comparable with both concentrations, and the lower concentration has the advantage of lower weight of the finished product.

After evaluating the level of coating to be applied in order to achieve 24 hours profile, it was concluded that the minimum level is 15% of the cores weight. The dissolution results of the different studied trials showed that plasticized films of the used polymer Kollicoat SR 30D are more mature films and give more robust behavior with time during storage and upon exposure to heat or moisture. So, in the contrary to manufacturer recommendations; Kollicoat SR 30D should be plasticized for better functionality.

Thermal curing affected the films without plasticizer causing release to be decreased, while plasticized films were not affected.

Accelerated conditions study showed that the polymeric coating is sensitive to moisture more than temperature, since moisture caused more significant retardation in dissolution.

Accordingly, it is recommended with Kollicoat SR 30D coatings to use plasticizer and to protect the finished product from moisture by choosing protective packaging material.

6. References

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7. Appendix (Dissolution tables)

Table 16: effect of curing on the release profiles of 8% unplasticized coated pellets

Time (hrs)	Average % Release ± SD	
	8% coating	8% Cured
0.5	36.6 ±6	19.2 ±1.3
1	59.1 ±2.9	38.9 ±2.3
2	84.5 ±6.7	72.5 ±0.4
4	96.4 ±1	93.1 ±0.4
6	99.3 ±0.7	97.7 ±1.7
8	100.7 ±0.5	100.7 ±1.1
10	103.0 ±0.4	100.4 ±0.7
12	102.1 ±3.2	100.5 ±1.1
16	104.2 ±2	100.5 ±2
20	102.8 ±2	101.2 ±1
24	101.5 ±0.4	102.0 ±0.6

Table 17: effect of curing on the release profiles of 8% plasticized coated pellets

Time (hrs)	Average % Release ± SD	
	8%+TEC	8%+TEC Cured
0.5	15.0 ±3	10.9 ±0.7
1	25.7 ±1.5	21.5 ±0.4
2	59.1 ±0.9	55.3 ±1
4	84.5 ±1.7	80.9 ±2.1
6	92.9 ±2	92.1 ±1
8	98.2 ±2.5	96.4 ±1.5
10	100.4 ±3.2	99.4 ±1.6
12	101.6 ±2.3	100.9 ±1.6
16	103.2 ±2.4	102.7 ±1.5
20	103.2 ±2.7	103.7 ±1.8
24	102.0 ±3.5	103.3 ±1.8

Table 18: effect of curing on the release profiles of 15% plasticized coated pellets

Time (hrs)	Average % Release ± SD	
	15%+TEC	15%+TEC Cured
0.5	8.0 ±0.4	10.0 ±0.15
1	8.6 ±1	10.7 ±0.7
2	16.3 ±0.5	16.6 ±1.2
4	35.2 ±0.6	32.7 ±1.2
6	51.6 ±0.6	51.5 ±0.4
8	63.5 ±0.2	65.2 ±2.5
10	72.6 ±1.5	73.8 ±1.5
12	78.5 ±0.2	79.8 ±1.5
16	88.6 ±3.2	90.9 ±0.4
20	95.0 ±5	96.0 ±2.2
24	99.7 ±0.5	100.3 ±1.2

Table 19: effect of curing on the release profiles of 15% unplasticized coated pellets

Time (hrs)	Average % Release ± SD	
	15% coating	15% Cured
0.5	3.6 ±0.8	2.3 ±0.2
1	4.7 ±0.6	2.97 0.04
2	22.8 ±2.5	18.2 ±0.6
4	53.6 ±4.5	43.0 ±0.6
6	70.8 ±2.8	59.1 ±0
8	81.4 ±2.3	74.4 ±0.4
10	86.8 ±2.3	85.1 ±0.4
12	91.4 ±2.1	90.7 ±0.8
16	96.9 ±0.6	99.2 ±2
20	98.8 ±1	103.6 ±3.3
24	99.01 2.9	104.2 ±0.3

Table 20: effect of curing on the release profiles of 22% plasticized coated pellets

Time (hrs)	Average % Release ± SD	
	22%+ TEC	22%+ TEC Cured
0.5	2.7 ±0.5	2.8 ±0.5
1	3.3 ±0.3	3.1 ±0.2
2	4.7 ±0.3	4.7 ±0.3
4	7.6 ±0.4	6.7 ±0.3
6	12.0 ±1.5	10.2 ±0.7
8	17.9 ±2.2	16.2 ±0.6
10	23.9 ±3	24.1 ±0.6
12	33.0 ±8	32.5 ±0.9
16	48.4 ±5	49.3 ±0.7
20	68.9 ±5.8	65.7 ±0.6
24	80.5 ±1.4	80.7 ±1

Table 21: effect of curing on the release profiles of 22% unplasticized coated pellets

Time (hrs)	Average % Release ± SD	
	22% Cured	22% coating
0.5	**1.7** ±0.3	**2.2** ±0.4
1	**2.6** ±1.6	**2.3** ±0.1
2	**4.2** ±0.6	**7.0** ±0.5
4	**13.3** ±0.6	**25.3** ±1.2
6	**22.6** ±1	**35.2** ±1.8
8	**31.0** ±1.5	**46.0** ±2.3
10	**39.8** ±1.2	**55. 6**±2
12	**48.5** ±1.7	**65.2** ±2.5
16	**67.2** ±1.8	**80.1** ±0.8
20	**82.9** ±5.3	**91.1** ±0.4
24	**94.0** ±7.5	**95.6** ±1.6

Table 22: Dissolution profiles for pellets with different levels of unplasticized coating.

Time (hrs)	Average % Release		
	8% coating	15% coating	22% coating
0.5	36.6	3.603	2.242
1	59.1	4.730	2.334
2	84.5	22.810	7.076
4	96.4	53.677	25.360
6	99.3	70.884	35.253
8	100.7	81.442	46.047
10	103.0	86.836	55.996
12	102.1	91.452	65.226
16	104.2	96.914	80.138
20	102.8	98.853	91.174
24	101.5	99.019	95.661

Table 23: dissolution profiles for pellets with different levels of plasticized coating

Time (hrs)	Average % Release		
	8%+ TEC	15%+TEC	22%+ TEC
0.5	15.0	8.012	2.736
1	25.7	8.627	3.364
2	59.1	16.300	4.701
4	84.5	35.248	7.680
6	92.9	51.602	12.040
8	98.2	63.584	17.988
10	100.4	72.609	23.936
12	101.6	78.509	33.096
16	103.2	88.670	48.433
20	103.2	95.040	68.993
24	102.0	99.752	80.532

Table 24: effect of plasticizer on the release profile of 8% coated pellets

Time (hrs)	Average % Release	
	8%+ TEC	8% coating
0.5	15.0	36.6
1	25.7	59.1
2	59.1	84.5
4	84.5	96.4
6	92.9	99.3
8	98.2	100.7
10	100.4	103.0
12	101.6	102.1
16	103.2	104.2
20	103.2	102.8
24	102.0	101.5

Table 25: effect of plasticizer on the release profile of 15% coated pellets

Time (hrs)	Average % Release	
	15%+TEC	15% coating
0.5	8.012	3.603
1	8.627	4.730
2	16.300	22.810
4	35.248	53.677
6	51.602	70.884
8	63.584	81.442
10	72.609	86.836
12	78.509	91.452
16	88.670	96.914
20	95.040	98.853
24	99.752	99.019

Table 26: effect of plasticizer on the release profile of 22% coated pellets

Time (hrs)	Average % Release	
	22%+ TEC	22% coating
0.5	2.736	2.242
1	3.364	2.334
2	4.701	7.076
4	7.680	25.360
6	12.040	35.253
8	17.988	46.047
10	23.936	55.996
12	33.096	65.226
16	48.433	80.138
20	68.993	91.174
24	80.532	95.661

Table 27: thermal stability results of 8% unplasticized coating

Time (hrs)	Average % Release						
	8% coating	one month Open	one month Closed	Two month Open	Two month Closed	Three month Open	Three month Closed
0.5	36.6	9.06	19.4	NA	NA	11.7	19.5
1	59.1	27.57	41.6	NA	NA	28.9	37.1
2	84.5	59.37	72.2	NA	NA	55.1	65.4
4	96.4	83.43	93.5	NA	NA	79.0	86.8
6	99.3	96.07	101.9	NA	NA	87.5	94.5
8	100.7	100.40	105.6	NA	NA	91.6	97.5
10	103.0	102.05	107.5	NA	NA	94.5	99.2
12	102.1	104.67	110.1	NA	NA	95.3	100.2
16	104.2	108.76	113.4	NA	NA	95.8	101.0
20	102.8	109.49	114.7	NA	NA	97.5	102.4
24	101.5	110.21	117.0	NA	NA	97.3	103.3

Table 28: thermal stability results of 8% plasticized coating

Time (hrs)	Average % Release						
	8%+ TEC	one month Open	one month Closed	Two month Open	Two month Closed	Three month Open	Three month Closed
0.5	15.0	NA	NA	12.7	NA	11.3	10.3
1	25.7	20.4	20.6	18.4	13.7	18.0	17.9
2	59.1	47.7	51.9	43.9	27.2	47.2	46.6
4	84.5	79.6	80.6	74.6	57.6	75.7	73.1
6	92.9	90.9	89.8	84.6	84.9	86.5	82.2
8	98.2	96.4	94.7	92.4	96.3	90.5	87.9
10	100.4	100.7	97.7	94.0	101.4	93.4	89.7
12	101.6	102.5	99.5	94.5	103.8	95.4	90.7
16	103.2	105.5	100.9	96.2	106.2	96.7	92.8
20	103.2	105.5	100.9	98.6	107.0	97.7	94.1
24	102.0	105.1	101.3	97.0	107.1	100.1	94.0

Table 29: thermal stability results of 15% unplasticized coating

Time (hrs)	Average % Release						
	15% coating	one month Open	one month Closed	Two month Open	Two month Closed	Three month Open	Three month Closed
0.5	3.603	1.4	2.2	3.6	2.7	2.4	2.5
1	4.730	2.1	3.7	2.6	5.4	2.2	3.6
2	22.810	4.7	21.9	5.6	23.5	2.8	17.1
4	53.677	17.1	51.8	10.3	54.0	8.0	47.6
6	70.884	42.1	73.6	33.4	74.3	24.8	69.5
8	81.442	63.4	84.2	61.0	84.7	50.2	78.9
10	86.836	78.7	89.6	82.2	91.6	71.0	85.1
12	91.452	86.4	93.5	92.8	95.2	83.1	89.6
16	96.914	95.4	98.8	100.2	100.8	91.2	94.1
20	98.853	99.3	100.7	102.7	101.8	94.2	96.5
24	99.019	101.0	103.2	103.5	102.9	95.7	97.1

Table 30: thermal stability results of 15% plasticized coating

Time (hrs)	Average % Release						
	15%+TEC	one month Open	one month Closed	Two month Open	Two month Closed	Three month Open	Three month Closed
0.5	8.012	10.3	12.1	11.4	11.3	12.3	11.0
1	8.627	11.8	14.6	10.3	11.2	11.2	10.8
2	16.300	16.1	20.9	12.6	19.6	12.4	17.1
4	35.248	19.6	34.4	16.9	33.1	15.7	31.1
6	51.602	27.9	52.3	21.9	52.0	22.7	48.0
8	63.584	43.6	67.5	35.0	67.7	37.6	65.5
10	72.609	62.8	78.8	56.2	78.0	59.5	76.9
12	78.509	78.5	84.9	78.2	84.2	77.1	85.2
16	88.670	92.4	92.6	97.1	91.9	91.2	89.1
20	95.040	97.7	95.6	103.1	94.4	93.4	94.0
24	99.752	98.2	97.7	96.6	103.5	94.8	94.1

Table 31: thermal stability results of 22% unplasticized coating

Time (hrs)	Average % Release						
	22% coating	one month Open	one month Closed	Two month Open	Two month Closed	Three month Open	Three month Closed
0.5	2.242	1.3	1.4	2.8	3.0	2.1	2.0
1	2.334	1.6	2.0	1.5	1.9	2.6	2.8
2	7.076	2.1	5.7	1.7	5.9	2.1	5.3
4	25.360	3.7	21.6	2.0	23.0	2.7	18.8
6	35.253	5.4	34.1	3.2	38.1	3.6	34.2
8	46.047	10.2	49.1	5.1	53.9	5.7	49.9
10	55.996	20.4	62.9	10.5	68.0	10.6	65.5
12	65.226	34.3	72.0	22.1	78.1	21.2	74.9
16	80.138	63.8	83.3	54.5	89.0	51.1	87.7
20	91.174	83.3	89.2	87.1	93.2	77.1	92.5
24	95.661	95.0	93.1	98.2	97.3	90.8	95.3

Table 32: thermal stability results of 22% plasticized coating

Time (hrs)	Average % Release						
	22%+ TEC	one month Open	one month Closed	Two month Open	Two month Closed	Three month Open	Three month Closed
0.5	2.7	3.3	3.2	3.8	2.8	4.4	4.6
1	3.4	4.9	4.9	4.8	4.1	4.7	5.0
2	4.7	6.2	7.4	5.7	6.1	5.5	6.7
4	7.7	7.6	10.5	6.6	10.2	6.3	9.9
6	12.0	8.2	16.3	7.6	13.2	6.9	14.8
8	18.0	10.1	26.7	8.6	26.6	8.3	24.6
10	23.9	13.3	38.2	11.3	40.0	11.4	36.3
12	33.1	21.5	50.7	17.6	51.6	18.7	48.9
16	48.4	48.1	70.9	41.3	72.2	45.1	69.1
20	69.0	77.5	84.2	72.4	85.3	75.5	83.3
24	80.5	94.1	93.3	90.8	89.9	89.1	88.9

تقييم شكل صيدلاني عديد الحبيبات طويل المفعول من دواء عالي الجرعة و عالي الذائبية في الماء باستعمال تقنية الرش السفلي (Wurster Column)

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الملخص

الهدف من هذا العمل هو تقييم إمكانية تصنيع شكل صيدلاني مضبوط المفعول ، متعدد الطبقات ، عديد الحبيبات من دواء عالي الجرعة و عالي الذائبية في الماء (Diltiazem HCl).

هذا الشكل الصيدلاني تم تصنيعه بواسطة رش الدواء على حبيبات جاهزة من السكر ، ثم رش الغطاء الضابط للإفراز باستعمال تقنية الرش السفلي (Wurster Column) .

عملية إضافة الدواء تمت برش المحلول المحتوي على الدواء الذائب و البوليمر على حبيبات السكر.

تم تحضير الحبيبات المحتوية على الدواء بثلاث مستويات من الدواء (30 ، 60 ، 120) بالمئة ، وتم استعمال kollicoat IR بمستويين نسبة إلى الدواء (5:1 و 5:2) ولم يكن لذلك تأثير على فعالية التصيع ؛ حيث أنه تم الحصول على نسبة تحميل عالية للدواء (120 %) على حبيبات السكر بغض النظر عن كمية البوليمر في المحلول و بكفاءة عالية .

تم اختيار الحبيبات المحتوية على الدواء بنسبة 120% و الكمية الأقل من البوليمر للانتقال بها إلى مرحلة التلبيس ، حيث تم إضافة ثلاث مستويات من Kollicoat SR (8 ، 15 ، 22 بالمئة) من وزن الحبيبات ، مرة بوجود ملدّن (TEC) و مرة بدون وجوده . بالإضافة إلى ذلك تم دراسة تأثير المعالجة بالحرارة على سرعة الإفراز من المستحضر النهائي .

ثم دراسة سرعة إفراز المادة الفعالة من الحبيبات الملبسة و الحبيبات غير الملبسة . الافراز من الحبيبات غير الملبسة كان مباشراً و كاملاً خلال 15 دقيقة .

تبين من نتائج الإفراز للحبوب الملبسة أنه كلما زاد مستوى التلبيس قلت سرعة الإفراز للدواء ، وتبين أيضاً أن إضافة المادة الملدنة تقلل أيضاً من سرعة الإفراز .

تأثير المعالجة الحرارية كان واضحاً في الحبيبات الملبسة بدون مادة ملدنة ، بينما الحبيبات الملبسة مع مادة ملدنة لم تتأثر بالحرارة .

تم أيضاً تقييم تأثير الحرارة و الرطوبة على ثباتية إفراز الدواء من الحبيبات الملبسة ، بينت النتائج أن تعرض الحبيبات الملبسة للحرارة و الرطوبة العالية يقلل من سرعة إفراز الدواء .